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JCO7 Rec'd PCT/PTO 06 APR 2001

SUBSTITUTE FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 06501-075001												
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (If Known, see 37 CFR 1.5) <b>09/807132</b>												
INTERNATIONAL APPLICATION NO. PCT/JP99/05578	INTERNATIONAL FILING DATE 8 October 1999	PRIORITY DATE CLAIMED 9 October 1998												
TITLE OF INVENTION NOVEL G PROTEIN-COUPLED RECEPTORS														
APPLICANT(S) FOR DO/EO/US Masatsugu Maeda, Yasuhiko Nakata and Hitoshi Nomura														
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:														
<p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).</p> <p>4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input type="checkbox"/> have been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input checked="" type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> <p><b>Items 11 to 16 below concern other documents or information included:</b></p> <p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</p> <p><input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input type="checkbox"/> Other items or information:</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>														
<table border="1"><tr><td colspan="2">CERTIFICATE OF MAILING BY EXPRESS MAIL</td><td>Express Mail Label No <b>EL624270785US</b></td></tr><tr><td colspan="3">I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231</td></tr><tr><td><b>April 6, 2001</b></td><td><i>Samantha Bell</i></td><td><i>Samantha Bell</i></td></tr><tr><td>Date of Deposit</td><td>Signature</td><td>Typed Name of Person Signing</td></tr></table>			CERTIFICATE OF MAILING BY EXPRESS MAIL		Express Mail Label No <b>EL624270785US</b>	I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231			<b>April 6, 2001</b>	<i>Samantha Bell</i>	<i>Samantha Bell</i>	Date of Deposit	Signature	Typed Name of Person Signing
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U.S. APPLICATION NO. (IF KNOWN) <b>09/807132</b>		INTERNATIONAL APPLICATION NO. PCT/JP99/05578		ATTORNEY'S DOCKET NUMBER 06501-075001	
17. <input type="checkbox"/> The following fees are submitted: <b>Basic National Fee ( 37 CFR 1.492(a)(1)-( 5) ):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... <b>\$1000</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$860</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$710</b>  International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$690</b>  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100</b>  <div style="text-align: right;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>				<b>CALCULATIONS</b> PTO USE ONLY	
				\$860.00	
				\$0.00	
				\$0.00	
Surcharge of <b>\$130</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total Claims	17 - 20 =	0	x <b>\$18</b>	\$0.00	
Independent Claims	2 - 3 =	0	x <b>\$80</b>	\$0.00	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ <b>\$270</b>	\$0.00	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$860.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$0.00	
<b>SUBTOTAL =</b>				\$860.00	
Processing fee of <b>\$130</b> for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				\$0.00	
<b>TOTAL NATIONAL FEE =</b>				\$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +				\$40.00	
<b>TOTAL FEES ENCLOSED =</b>				\$900.00	
				<b>Amount to be refunded:</b>	\$
				<b>Charged:</b>	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$900.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive          (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO:					
Janis K. Fraser, Ph.D., J.D. FISH & RICHARDSON P.C. 225 Franklin Street Boston, MA 02110-2804 (617) 542-5070 phone (617) 542-8906 facsimile			SIGNATURE: <i>John T. Li</i>		
			NAME: John T. Li		
			REGISTRATION NUMBER: 44,210		

09/807132

Attorney's Docket No.: 06501-075001 / C2-012DP1PCT-US

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Masatsugu Maeda et al. Art Unit : Unknown  
Serial No. : Examiner : Unknown  
Filed : April 6, 2001  
Title : NOVEL G PROTEIN-COUPLED RECEPTORS

Commissioner for Patents  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the claims:

Please replace the following claims:

4. (Amended) A DNA encoding the protein or peptide of claim 1.
7. (Amended) A method of producing a protein or peptide comprising the steps of: cultivating the transformant of claim 6, and recovering the protein or peptide expressed therein.
8. (Amended) A method of screening for a compound that is capable of binding to the protein of claim 1, comprising the steps of:
  - (a) exposing a test sample to the protein or peptide of claim 1, and
  - (b) selecting the compound that binds to the protein or peptide of claim 1.

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April 6, 2001

Signature

Samantha Bell  
Typed or Printed Name of Person Signing Certificate

- (a) exposing a test sample to a cell expressing the protein or peptide of any of claims 1 to 3 on its surface,
- (b) measuring a biochemical change in said cell, and
- (c) selecting the compound that induces said biochemical change in said cell.

11. (Amended) A method of detecting or measuring a protein or peptide comprising the steps of: exposing the antibody of claim 10 to a sample which is assumed to comprise said protein or peptide, and detecting or measuring the generation of an immune complex between said antibody and said protein or peptide.

Applicant : Masatsugu Maeda et al.  
Serial No. :  
Filed :  
Page : 3

Attorney's Docket No.: 06501-075001 /  
C2-012DP1PCT-US

REMARKS

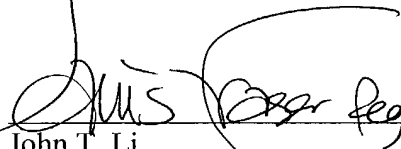
Claims 1 to 12 are pending in this application, claims 4, 7, 8, 9 and 11 having been amended to delete multiple dependency. No new matter has been added.

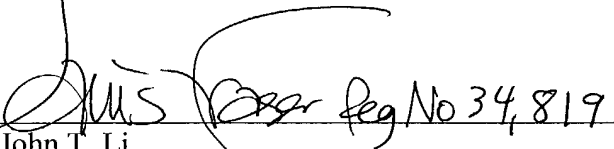
Attached is a marked-up version of the changes being made by the current amendment.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 6, 2001

  
John T. Li  
Reg. No. 44,210

  
Reg No 34,819

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Boston, MA 02110-2804  
Telephone: (617) 542-5070  
Facsimile: (617) 542-8906

**Version with markings to show changes made**

**In the claims:**

4. (Amended) A DNA encoding the protein or peptide of [any of claims 1 to 3]  
claim 1.
7. (Amended) A method of producing [the] a protein or peptide [of any of  
claims 1 to 3,] comprising the steps of: cultivating the transformant of claim 6, and  
recovering the protein or peptide expressed therein.
8. (Amended) A method of screening for a compound that is capable of binding  
to the protein of claim 1, comprising the steps of:
  - (a) exposing a test sample to the protein or peptide of [any of claims 1 to 3]  
claim 1, and
  - (b) selecting the compound that binds to the protein or peptide of [any of claims 1  
to 3] claim 1.
9. (Amended) A method of screening for a ligand and/or agonist that is capable  
of binding to the protein of claim 1, comprising the steps of:
  - (a) exposing a test sample to a cell expressing the protein or peptide of [any of  
claims 1 to 3] claim 1 on its surface,
  - (b) measuring a biochemical change in said cell, and
  - (c) selecting the compound that induces said biochemical change in said cell.
11. (Amended) A method of detecting or measuring [the] a protein or peptide  
[of any of claims 1 to 3,] comprising the steps of: exposing the antibody of claim 10 to a  
sample which is assumed to comprise said protein or peptide, and detecting or measuring  
the generation of an immune complex between said antibody and said protein or peptide.

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## DESCRIPTION

## NOVEL G PROTEIN-COUPLED RECEPTORS

5 Technical Field

The present invention relates to novel G protein-coupled receptor proteins and their genes, as well as methods for producing and using same.

10 Background Art

The olfactory receptor (OR) gene family has been known as a multiple gene family encoding odorant receptors that govern the system for olfactory response in the living body. A member of the gene family was first reported to be expressed in rat olfactory neurons in 1991 (Buck L. et al. Cell 65:175-187 (1991)), and subsequently, a number of homologous genes were found across species, in canine (Permentier M. et al. Nature 355:453-455 (1992)), mouse (Ressler K.J. et al. Cell 73:597-609 (1993)), human (Selbie L.A. et al. Mol. Brain Res. 13:159-163 (1992)), catfish (Ngai J. et al. Cell 72:657-666 (1993)), and frog (Freitag J. et al. Neuron 15:1383-1392 (1995)). The receptor proteins encoded by the genes of the family have a unique seven transmembrane structure that is similar to other G protein-coupled receptor subfamilies, and their first extracellular domain contains a common [N-x-S/T] motif (x: any amino acid) which is modified by sugar. Their second and third extracellular domains, loop-1 and loop-2, respectively, are cross-linked by a disulfide bond between the conserved cysteine residues of each. The [M-A-Y-D-R-Y-L/V-A-I/V-C] sequence within the second intracellular domain is another common motif predicted to be functionally important. Especially, the [D-R-Y] motif is suggested to be essential for the binding to intracellular G proteins (Rosenthal W. et al. J. Biol. Chem. 268:13030-13033 (1993); Marchese A. et al. Genomics 23:609-618 (1994)).

Although it is predicted that there exist ligands for the odorant receptor family, such as odour ligands and neuropeptide-like molecules, the exact nature has remained obscure (Buck L. et al. Cell 65:175-187 (1991); Ngai J. et al. Cell 72:657-666 (1993)). Little is known about

their signal transduction except for coupling with G proteins, and thus functional analysis of the gene family is desired. Recently, it has been proposed to classify the entire gene family into eight subfamilies according to structural similarity. However, it is unlikely that the classification itself can reflect functional similarity among the genes. In human, it is assumed that approximately one thousand copies of this gene family exists. However, about 70% of the copies are assumed to be pseudo genes (Sylvie R. et al. Nature Gen. 18:243-250 (1998)).

#### Disclosure of the Invention

The present invention provides novel G protein-coupled receptor proteins and their genes, as well as materials and methods for producing them, molecules used for the method and such, and their use.

The present inventors performed BLAST search of the GenBank public database and found multiple human genome sequences that encode novel seven transmembrane G protein-coupled receptor genes. The inventors carried out RT-PCR using oligonucleotide primers that were designed based on the above genome sequences and mRNA prepared from human tissues as a template, and obtained partial cDNA sequences of the target genes. This RT-PCR was also used to evaluate the expression pattern and profile of the genes in those tissues. Then, the inventors carried out 5'- and 3'- RACE using a cDNA library prepared from human testis as a template, in which the genes were highly expressed based on the result of RT-PCR, and succeeded in isolating the full length cDNA. The first three genes isolated, originating from human chromosome 14, are designated as GTAR14-1, GTAR14-3, and GTAR14-5, and the next four genes isolated, originating from human chromosome 11, are designated as GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4.

These genes encode novel seven transmembrane G protein-coupled receptors, and fulfill the characteristics of the known olfactory receptor family genes. The result of the analysis of gene expression in human tissues showed that GTAR14-1 was detected strongly in lymphatic/hematopoietic tissues, including thymus and spleen, testis, and pancreas, and was also expressed in fetal thymus. GTAR14-3 was detected strongly in thymus and testis, but was also expressed widely



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in multiple tissues, including digestive tissues such as small intestine and colon, and hormone secreting tissues such as placenta and prostate. GTAR14-5 was detected strongly in lymphatic/hematopoietic tissues, such as thymus, spleen, and peripheral leukocytes, and testis. Its expression was intensified in fetal thymus, fetal spleen, and fetal lung, and was detected weakly in fetal brain and fetal kidney. GTAR11-1 was detected strongly in lymphatic/hematopoietic tissues including thymus, spleen, and peripheral lymphocytes, digestive tissues such as small intestine and colon, and testis and placenta. GTAR11-2 was detected strongly in lymphatic/hematopoietic tissues including thymus and peripheral lymphocytes, and testis and placenta. GTAR11-3 was detected strongly in lymphatic/hematopoietic tissues including thymus and spleen, and genital organs, and was also detected broadly in multiple tissues including digestive tissues such as small intestine and colon, muscle, and neuronal tissues. GTAR11-4 was detected strongly in lymphatic/hematopoietic tissues including thymus and spleen, and genital organs, and was also extensively expressed in multiple tissues including digestive tissues such as small intestine and colon, and endocrine tissues.

These expression profiles suggest that proteins encoded by those genes have an important function in lymphatic/hematopoietic and endocrine tissues. Consequently, it was considered that the proteins can be used for screening a novel hematopoietic peptide factor or a novel hormone-like peptide factor.

The present invention relates to novel G protein-coupled receptor proteins and their genes, and their production and use as well. More specifically, it provides:

(1) a G protein-coupled receptor protein selected from the group consisting of:

(a) a protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 5, 6, 28, 29, 30, and 31;

(b) a protein of (a), wherein one or more amino acids are modified by deletion, addition, insertion, and/or substitution by another amino acid residue; and

(c) a protein encoded by DNA that hybridizes with DNA having

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a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 24, 25, 26, and 27;

(2) a fusion protein comprising the protein of (1) and another peptide or polypeptide;

5 (3) a peptide comprising a part of the protein of (1);

(4) a DNA encoding the protein or peptide of any of (1) to (3);

(5) a vector comprising the DNA of (4) inserted therein;

10 (6) a transformant carrying the DNA of (4) in an expressible manner;

(7) a method of producing the protein or peptide of any of (1) to (3), comprising the steps of: cultivating the transformant of (6), and recovering the protein or peptide expressed therein;

15 (8) a method of screening for a compound that is capable of binding to the protein of (1), comprising the steps of:

(a) exposing a test sample to the protein or peptide of any of (1) to (3); and

(b) selecting the compound that binds to the protein or peptide of any of (1) to (3);

20 (9) a method of screening for a ligand and/or agonist that is capable of binding to the protein of (1), comprising the steps of:

(a) exposing a test sample to a cell expressing the protein or peptide of any of (1) to (3) on its surface;

25 (b) measuring a biochemical change in said cell; and

(c) selecting the compound that induces said biochemical change in said cell;

(10) an antibody that binds to the protein of (1);

30 (11) a method of detecting or measuring the protein or peptide of any of (1) to (3), comprising the steps of: exposing the antibody of (10) to a sample which is assumed to comprise said protein or peptide, and detecting or measuring the generation of an immune complex between said antibody and said protein or peptide; and

35 (12) A DNA of a length of 15 nucleotides or longer that hybridizes with a DNA having a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 24, 25, 26, 27, and their

complementary strands.

The nucleotide sequences of GTAR14-1, GTAR14-3, and GTAR14-5 cDNAs that were isolated by the present inventors, and the amino acid sequences of the proteins encoded by the cDNAs are shown in SEQ ID NO: 1, 2, 3, 4, 5, and 6, respectively. The nucleotide sequences of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 cDNAs that were also isolated by the present inventors, and the amino acid sequences of the proteins encoded by the cDNAs are shown in SEQ ID NOs: 24, 25, 26, 27, 28, 29, 30, and 31, respectively.

The receptor proteins of the OR gene family have a seven transmembrane type structure like other G protein-coupled receptors, and their first extracellular domains have a [N-x-S/T] motif (x: any amino acid) in common that is modified by sugar. There are conserved cysteine residues in the second (loop-1) and third (loop-2) extracellular domains that form a disulfide bond for cross-linking. Furthermore, there is a [M-A-Y-D-R-Y-L/V-A-I/V-C] sequence (especially [D-R-Y] motif) in the second intracellular domain, which is suggested to be essential for binding to the G protein (Rosenthal W. et al. J. Biol. Chem. 268:13030-13033 (1993); Marchese A. et al. Genomics 23:609-618 (1994)).

The seven proteins encoded by the seven genes isolated by the present inventors (designated as GTAR proteins below) are cell membrane proteins and are seven transmembrane receptors that contain seven hydrophobic transmembrane domains.

GTAR proteins, like known odorant receptors, have the above described motifs characteristic to G protein-coupled receptors. The [N-x-S/T] motif (x: any amino acid) modified by sugar is found within the first extracellular domain as [N-Q-T], [N-S-T], and [N-T-S] in GTAR14-1, GTAR14-3, and GTAR14-5 proteins, respectively, as [N-Y-S] in GTAR11-1 protein, and as [N-S-T] in GTAR11-2, GTAR11-3, and GTAR11-4 proteins.

GTAR proteins have conserved cysteine residues in the second and third extracellular domains (loop-1 and loop-2, respectively). Furthermore, they have the [M-A-Y-D-R-Y-L/V-A-I/V-C] sequence in the second intracellular domain, which is suggested to be essential for binding to G protein, as well: [V-A-Y-D-R-Y-V-A-I-C] in GTAR14-1

protein, and [M-A-Y-D-R-Y-L-A-I-C] in all the others.

These features suggest that GTAR proteins of the present invention, like other G protein-coupled receptor proteins, function through binding to intracellular G proteins in response to the stimuli of extracellular ligands.

Furthermore, the result of RT-PCR analysis revealed a strong expression of GTAR genes in thymus and testis (See, for example, Example 1(3) and 2(3), Figures 7 to 9, and Figures 20 to 23). This suggests that the GTAR proteins of the present invention may regulate the differentiation, or proliferation and activation of a particular group of lymphatic cells. Thus, GTAR proteins could function as a central molecule that controls the activities characteristic to lymphocytes through interaction with G proteins in response to ligand stimuli. As these proteins are expressed in testis, where cells are changing continuously in the cell cycle at a high turn over rate, it is possible that they regulate cell cycle and cell division.

On the other hand, the expression of GTAR14-1 gene was detected in spleen, where hematopoietic cells are expected to exist. The GTAR14-5 gene was also expressed in spleen and peripheral leukocytes, where hematopoietic cells are thought to be contained. The GTAR11 genes were expressed in peripheral leukocytes, in which hematopoietic cells are considered to be included, and furthermore the genes for GTAR11-1, GTAR11-3, and GTAR11-4 were expressed in spleen, which is expected to have hematopoietic cells. These suggest that GTAR proteins, particularly GTAR14-1, GTAR14-5, and GTAR11 proteins, which have structural similarities to known odorant receptors, could function as a receptor for a novel hematopoietic regulator.

The GTAR14-3 gene was expressed in thymus and testis as described above, and also in digestive tissues, including small intestine and colon, and endocrine organs, such as placenta and prostate. Moreover, the result of RT-PCR using mRNA prepared from human fetal tissues showed a broad distribution pattern of GTAR14-3 gene expression, with strong expression in thymus, brain, heart, smooth muscle, and kidney, and weak expression in fetal liver and fetal lung. This not only suggests that GTAR14-3 protein can function as a receptor of a novel hematopoietic factor, but also strongly suggests that the protein

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could regulate diverse physiological functions as a receptor of a novel hormone-like peptide molecule.

The GTAR proteins of the present invention, which can play a central role in the function of immune responsive cells, may find  
5 utility in clinical treatment of the following field of diseases.

First, it is possible to enhance the cellular immune system of the living body by promoting the activity of GTAR proteins through *in vivo* administration of (1) a ligand or agonist derived from the living body that is capable of functionally binding to GTAR proteins,  
10 or (2) a specific antibody that can activate the function of GTAR proteins. Such substances that are capable of functionally binding to GTAR proteins can be clinically applied as a growth promoting factor, a differentiation inducing factor, or an activator of immune cell functions in immune responsive cells, especially in the group of T-cells.  
15 This means that they can promote *in vivo* immune response, including anti tumor immunity and anti infection immunity. More specifically, it is possible to enhance cytotoxic immunity toward a particular type of tumor tissue, and also increase resistance against a variety of viruses, including but not limited to HCV and HIV, by enhancing anti  
20 infection immunity in the living body.

Next, it is possible to suppress the cellular immunity in the living body by promoting the inhibition of the activity of GTAR proteins through *in vivo* administration of (1) an antagonist or inhibitor that is capable of functionally binding to GTAR proteins, or (2) a specific  
25 antibody that can inhibit the function of GTAR proteins. Such substances that are capable of functionally binding to GTAR proteins can be clinically applied as a growth inhibiting factor, a differentiation inhibiting factor, or a suppressor of immune cell functions of immune responsive cells, especially of the group of T-cells.  
30 Thus, they can suppress autoimmune diseases resulting from self damaging, and rejection reactions accompanying tissue transplantation, a most critical issue in transplantation immunity. More specifically, they are expected to be very effective for diseases including, but not limited to, diabetes, liver damage, collagen arthritis, GVHD, and EAE, all of which are induced by abnormal activation of immune  
35 response. Immunosuppression by the inhibitors could also be

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effective for a variety of antigen specific allergies, such as metal allergy and pollen allergy .

The present invention further provides proteins that are functionally equivalent to the GTAR proteins of the present invention.

5 Herein, "functionally equivalent" means that a protein has an equivalent biological activity to that of GTAR proteins. An illustrative biological activity is the ability of GTAR to act as a G protein-coupled receptor protein, which is an activity to interact with intracellular G proteins in response to ligand stimuli and  
10 transduce signals from outside to inside of cells.

A functionally equivalent protein may be obtained by introducing a mutation into the amino acid sequence of the protein. For instance, site-directed mutagenesis using synthetic oligonucleotide primers may be used to introduce a desired mutation (Kramer W. and Fritz H.J.  
15 Methods Enzymol. 154:350-367 (1987)). PCR mediated site-directed mutagenesis system (GIBCO-BRL) may also be used for introducing mutations into amino acid sequences of proteins. By using these methods, it is possible to obtain a functionally equivalent protein to GTAR proteins having an amino acid sequence of a GTAR protein (i.e.,  
20 SEQ ID NO: 4 to 6, and SEQ ID NO: 28 to 31) in which one or more amino acids are deleted, added, and/or substituted by other amino acid residues without affecting their biological activities.

More specifically, a functionally equivalent protein to GTAR proteins may have a sequence in which one or more, preferably two  
25 or more but not more than 30, more preferably two or more but not more than 10 amino acid residues are deleted from the amino acid sequence of SEQ ID NOs: 4 to 6 or SEQ ID NOs: 28 to 31. A functionally equivalent protein to a GTAR protein of the present invention may have a sequence in which one or more, preferably two or more but not more than 30,  
30 more preferably two or more but not more than 10 amino acid residues are added to the amino acid sequence of SEQ ID NOs: 4 to 6 or SEQ ID NOs: 28 to 31. A functionally equivalent protein to a GTAR protein of the present invention may have a sequence in which one or more, preferably two or more but not more than 30, more preferably two or  
35 more but not more than 10 amino acid residues are substituted by other amino acids in the amino acid sequence of SEQ ID NOs: 4 to 6 or SEQ

ID NOs: 28 to 31.

It is well known that a protein having deletion, addition, and/or substitution of one or more amino acid residues in the sequence of a protein can retain the original biological activity (Mark D.F. et al. Proc. Natl. Acad. Sci. U.S.A. 81:5662-5666 (1984); Zoller M.J. and Smith M. Nucleic Acids Res. 10:6487-6500 (1982); Wang A. et al. Science 224:1431-1433; Dalbadie-McFarland G. et al. Proc. Natl. Acad. Sci. U.S.A. 79:6409-6413 (1982)).

For instance, a protein in which one or more amino acid residues are added to GTAR proteins may be a fusion protein comprising GTAR proteins. The present invention provides for a fusion protein, wherein one or more GTAR proteins and one or more of another protein or peptide are fused. Conventional methods may be used to generate a fusion protein of the present invention. For example, a DNA encoding the GTAR protein and a DNA encoding the other protein or peptide are ligated so as to match their ORFs in the same frame, and introduced into an expression vector. The resulting fusion protein is then expressed in a host cell. The protein or peptide to be fused to the GTAR protein of the present invention is not limited to any specific protein or peptide.

For instance, known peptides including FLAG peptide (Hopp T.P. et al. BioTechnology 6:1204-1210 (1988)), 6xHis that is made up of six histidine residues, 10xHis, influenza hemagglutinin (HA), human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40 T antigen fragment, lck tag,  $\alpha$ -tubulin fragment, B-tag, and Protein C fragment may be used for fusion. Also, glutathione-S-transferase (GST), influenza hemagglutinin (HA), the constant region of immunoglobulin,  $\beta$ -galactosidase, maltose binding protein (MBP), and the like may be used as a protein to be fused. DNA encoding these proteins are known in the art and/or commercially available.

The present invention also provides proteins encoded by DNA that hybridizes with DNA having a nucleotide sequence of SEQ ID NOs: 1 to 3 or 24 to 27 under stringent conditions, and is functionally equivalent to GTAR proteins. Stringent conditions may be appropriately chosen by a skilled artisan, and include low stringent

conditions. Low stringent conditions may be, for example, at 42°C in 2x SSC and 0.1% SDS, preferably at 50°C in 2x SSC and 0.1% SDS. More preferably, high stringent conditions such as at 65°C in 2x SSC and 0.1% SDS may be chosen. DNA with higher homology can be obtained  
5 at higher temperature under these conditions.

Furthermore, the present invention provides proteins that are functionally equivalent to GTAR proteins and homologous to the amino acid sequence of the proteins (SEQ ID NOs: 4 to 6 and 28 to 31). In the context of the present invention, a protein is "homologous"  
10 provided it has at least 70% homology, preferably 80% or higher, more preferably 90% or higher, and even more preferably 95% or higher homology to an amino acid sequence of SEQ ID NOs: 4 to 6 or 28 to 31. The degree of homology between two proteins can be determined by using an algorithm described in the literature (Wilbur W.J. and Lipman D.J.  
15 Proc. Natl. Acad. Sci. U.S.A. 80:726-730 (1983)).

A protein of the present invention may have variations in amino acid sequence, molecular weight, isoelectric point, the presence or absence of sugar chains, or form, depending on the cell or host used to produce it or the purification method utilized. Nevertheless,  
20 as long as it has an activity as a G protein-coupled receptor, it is within the scope of the present invention.

A protein of this invention may be produced by inserting the obtained DNA into an expression vector and expressing under the regulation of an expression regulating region, such as an enhancer  
25 or promoter. The expression vector is used to transform a host cell, where the protein is expressed.

More specifically, for expression in mammalian host cells, one may construct a DNA or a vector in which a standard useful promoter/enhancer, a DNA encoding a protein of the invention, and  
30 a polyA signal at the 3' downstream are functionally integrated. For instance, human cytomegalovirus immediate early promoter/enhancer may be used as a promoter/enhancer.

Also, virus promoter/enhancers such as those of retrovirus, polyomavirus, adenovirus, and simian virus 40 (SV40), or mammalian  
35 promoter/enhancers such as that of human elongation factor 1 $\alpha$  (HEF1 $\alpha$ ) may be used as a promoter/enhancer for protein expression.



For instance, the SV40 promoter/enhancer may be readily used according to the method of Mulligan et al. (Nature 277:108 (1979)), and HEFl $\alpha$  promoter/enhancer may be readily used following the method of Mizushima et al. (Nucleic Acids Res. 18:5322 (1990)).

5 For expression in *E. coli*, a DNA may be constructed in which a standard useful promoter, a signal sequence for polypeptide secretion, and the gene to be expressed are functionally integrated. The promoter may be, for example, the LacZ promoter, the araB promoter, and the like. The LacZ promoter may be used according to the method of Ward  
10 et al. (Nature 341:544-546 (1998); FASEB J. 6:2422-2427 (1992)). The araB promoter may be used following the method of Better et al. (Science 240:1041-1043 (1988)).

For producing the protein in the periplasm of *E. coli*, the pelB signal sequence (Lei S.P. et al. J. Bacteriol. 169:4379 (1987)) may  
15 be used as a signal sequence.

The origin used for replication may be those of SV40, polyomavirus, adenovirus, bovine papilloma virus (BPV), and the like. In addition, the expression vector may include a selection marker gene for amplification of the gene copies in host cells. Examples of such  
20 markers include, but are not limited to, the aminoglycoside transferase (APH) gene, the thymidine kinase (TK) gene, the *E. coli* xanthine-guanine phosphoribosyl transferase (Ecogpt) gene, and the dihydrofolate reductase (dhfr) gene..

The expression vector for production of the protein of the  
25 invention is not limited to any specific one as long as it is suitably used for the purpose. For example, the expression vector may be a mammal-derived expression vector (e.g., pEF and pCDM8), an insect cell-derived expression vector (e.g., pBacPAK8), a plant-derived expression vector (e.g., pMH1 and pMH2), an animal virus-derived  
30 expression vector (e.g., pHSV, pMV, and pAdexLcw), a retrovirus-derived expression vector (e.g., pZipneo), an yeast-derived expression vector (e.g., pNV11 and SP-Q01), a *Bacillus subtilis*-derived expression vector (e.g., pPL608 and pKTH50), or an *E. coli*-derived expression vector (e.g., pQE, pGEAPP, pGEMEAPP, and  
35 pMALp2).

The vector of the present invention not only may be used for

producing the protein of the invention *in vivo* or *in vitro*, but also may be used for gene therapy in mammals including humans.

Known methods, such as calcium phosphate method (Virology 52:456-467 (1973)) and electroporation (EMBO J. 1:841-845 (1982)), may be used to introduce the expression vector constructed above into a host cells.

Any production system can be used herein for producing proteins. The present invention provides methods of producing a protein of the invention both *in vitro* or *in vivo*.

For *in vitro* production, eukaryotic cells or prokaryotic cells can be used. Useful eukaryotic cells may be animal, plant, or fungi cells. As animal cells, mammalian cells such as CHO (J. Exp. Med. 108:945 (1995)), COS, myeloma, baby hamster kidney (BHK), HeLa, or Vero cells, amphibian cells such as *Xenopus* oocytes (Valle et al. Nature 291:340-358 (1981)), or insect cells such as sf9, sf21, or Tn5 cells can be used. CHO cells lacking DHFR gene (dhfr-CHO) (Proc. Natl. Acad. Sci. U.S.A. 77:4216-4220 (1980)) or CHO K-1 (Proc. Natl. Acad. Sci. U.S.A. 60:1275 (1968)) may also be used.

As plant cells, plant cells originating from *Nicotiana tabacum* are known and may be used as callus cultures. As fungi cells, yeast cells such as *Saccharomyces*, including *Saccharomyces cerevisiae*, or filamentous fungi such as *Aspergillus*, including *Aspergillus niger*, are known and may be used herein.

Useful prokaryotic cells include bacterial cells, such as *E. coli* or *Bacillus subtilis*.

These cells are transformed by a desired DNA, and the resulting transformants are cultured *in vitro* to obtain the protein. Transformants can be cultured using known methods. Culture medium such as DMEM, MEM, RPMI1640, or IMDM may be used with or without serum supplement such as fetal calf serum (FCS). The pH of the culture medium is preferably between about 6 and 8. Such cells are typically cultured at about 30 to 40 °C for about 15 to 200 hr, and the culture medium may be replaced, aerated, or stirred if necessary.

Animal and plant hosts may be used for *in vivo* production. For example, a desired DNA can be introduced into an animal or plant host. Encoded proteins are produced *in vivo*, and then recovered. These

animal and plant hosts are included in host cells of the present invention.

Animals to be used for the production system described above include, but are not limited to, mammals and insects. Mammals such as goat, porcine, sheep, mouse, and bovine may be used (Vicki Glaser, SPECTRUM Biotechnology Applications (1993)). Alternatively, the mammals may be transgenic animals.

For instance, a desired DNA may be prepared as a fusion gene by inserting it into the middle of a gene, such as goat  $\beta$  casein gene which encodes a protein specifically produced into milk. DNA fragments comprising the fusion gene having the desired DNA are injected into goat embryos, which are then introduced back to female goats. Proteins are recovered from milk produced by the transgenic goats (i.e., those born from the goats that had received the modified embryos) or from their offspring. To increase the amount of milk containing the proteins produced by transgenic goats, appropriate hormones may be administered to them (Ebert K.M. et al. Bio/Technology 12:699-702 (1994)).

Alternatively, insects, such as the silkworm, may be used. A desired DNA inserted into baculovirus can be used to infect silkworms, and the desired protein is recovered from their body fluid (Susumu M. et al. Nature 315:592-594 (1985)).

As plants, for example, tobacco can be used. In use of tobacco, a desired DNA may be inserted into a plant expression vector, such as pMON530, which is introduced into a bacteria, such as *Agrobacterium tumefaciens*. Then the bacteria is used to infect tobacco, such as *Nicotiana tabacum*, and a desired polypeptide is recovered from their leaves (Julian K.-C. Ma et al. Eur. J. Immunol. 24:131-138 (1994)).

A protein of the present invention obtained as above may be isolated from inside or outside of cells or hosts, and purified as a substantially pure homogeneous protein. The method for protein isolation and purification is not limited to any specific method; in fact, any standard method may be used. For instance, column chromatography, filter, ultrafiltration, salt precipitation, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis,

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isoelectric point electrophoresis, dialysis, and recrystallization may be appropriately selected and combined to isolate and purify the protein.

For chromatography, for example, affinity chromatography, ion-exchange chromatography, hydrophobic chromatography, gel filtration, reverse phase chromatography, adsorption chromatography, and such may be used (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed. Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press (1996)). These chromatographies may be performed by liquid chromatography such as HPLC and FPLC. Thus, the present invention provides for highly purified proteins, produced by the above methods .

A protein of the present invention may be optionally modified or partially deleted by treating it with an appropriate protein modification enzyme before or after purification. Useful protein modification enzymes include, but are not limited to, trypsin, chymotrypsin, lysylendopeptidase, protein kinase, and glucosidase.

The present invention also provides partial peptides of the GTAR proteins of the present invention (i.e., SEQ ID NOs: 4 to 6 and 28 to 31). A partial peptide may be, for example, a peptide which is one of the partial peptide sequences encoded by GTAR genes, and corresponds to the binding domain to an *in vivo* ligand. Such a partial peptide, when administered *in vivo*, may bind to the ligand competitively, and inhibit the binding between the GTAR protein and the ligand. Similarly, a partial peptide corresponding to the G-protein binding domain of a GTAR protein may antagonistically inhibit the binding between GTAR protein and intracellular G protein. Such partial peptides may be useful as inhibitors of signal transduction pathways mediated by GTAR proteins.

A partial peptide of the protein of the invention can be produced by genetic engineering, known methods of peptide synthesis, or by digesting the protein of the invention with an appropriate peptidase. For peptide synthesis, for example, solid phase synthesis or liquid phase synthesis may be used.

Furthermore, the present invention relates to a DNA encoding the protein of the present invention as described. A cDNA encoding

A desired DNA fragment is prepared from the PCR products and ligated with a vector DNA. The recombinant vectors are used to transform *E. coli* and such, and a desired recombinant vector is prepared from a selected colony. The nucleotide sequence of the desired DNA is verified by conventional methods, such as dideoxynucleotide chain

termination.

A DNA of the invention may be designed to have a sequence that is expressed more efficiently by taking into account the frequency of codon usage in the host to be used for expression (Grantham R. et al. Nucleic Acids Res. 9:43-74 (1981)). The DNA of the present invention may be altered by a commercially available kit or a conventional method. For instance, the DNA may be altered by digestion with restriction enzymes, insertion of a synthetic oligonucleotide or an appropriate DNA fragment, addition of a linker, or insertion of the initiation codon (ATG) and/or the stop codon (TAA, TGA, or TAG).

The present invention particularly provides DNA having the following nucleotide sequences: from A at 9 to C at 947 of SEQ ID NO: 1, from A at 13 to T at 951 of SEQ ID NO: 2, from A at 410 to T at 1339 of SEQ ID NO: 3, from A at 17 to G at 892 of SEQ ID NO: 24, from A at 18 to C at 956 of SEQ ID NO: 25, from A at 18 to C at 956 of SEQ ID NO: 26, or from A at 19 to C at 945 of SEQ ID NO: 27.

Furthermore, the present invention provides DNA that is capable of hybridizing with DNA having a nucleotide sequence of SEQ ID NOs: 1 to 3 or 24 to 27 under stringent conditions, and encoding a protein functionally equivalent to the protein of the invention described above. Stringent conditions may be appropriately chosen by one skilled in the art. For instance, low stringent conditions may be 42°C in 2xSSC and 0.1% SDS, and preferably 50°C in 2xSSC and 0.1% SDS. More preferably, high stringent conditions such as 65°C in 2xSSC and 0.1% SDS may be chosen. Under the conditions, DNAs having higher homologies can be obtained with increasing temperature. The hybridizing DNA above is preferably a cDNA or a chromosomal DNA.

The protein of the invention may be used for screening a compound that is capable of binding to the protein, such compound being useful as a drug, or the like. Specifically, the protein may be used in a method of screening the compound, such method comprising the steps of exposing the protein of the present invention to a test sample in which a compound binding to the protein is expected to be contained, and selecting the compound having the activity of binding to the protein.

The proteins of the invention used for screening may be







cell lysates, etc. After loading the test sample, the column is washed, and proteins bound to the protein of the invention can be obtained.

Alternatively, a compound that binds to the protein of the invention may be screened by stably expressing the protein of the present invention on the surface of an appropriate host cell, exposing the cell to a sample which is assumed to contain a ligand, and detecting a biochemical change induced in the cell. The host cell may be one of a variety of mammalian cells, but preferably it is a cell which naturally express the protein of the invention, for example, the immune cells. Different biochemical changes may be used as an index, depending on the type of G proteins that bind to the protein of the invention. Examples include, but are not limited to, cAMP production, change in intracellular calcium concentration, and activation of protein kinase C. Alternatively, as a more generally used index, micro extracellular pH change can be measured by a microphysiometer (for instance, "Cytosensor<sup>R</sup>", Molecular Device Inc.).

Samples to be tested in the method for screening of the present invention include, but are not limited to, peptides, purified or crude preparation of proteins, non-peptide compounds, synthetic compounds, products of microorganism fermentation, cell extracts, animal tissue extracts, marine organism extracts, and plant extracts.

Compounds isolated by the above method for screening may be a candidate for a drug that can promote or inhibit the activity of the protein of the invention and thus be useful in the treatment of a disease caused by the abnormal function of a receptor protein of the invention. That part of the compound having the activity to bind to the protein of the present invention obtained by the method for screening of the present invention may be structurally changed by addition, deletion, and/or substitution. Such compound parts or fragments are also within the scope of the present invention.

It is possible to screen an agonist or antagonist of a receptor protein of the invention by using as an index the biochemical changes described above or the activity inhibiting the binding between the receptor protein and its ligand. Herein, an agonist is defined herein as a compound that is not derived from nature but is capable of binding to the protein(s) of the invention and inducing a physiological reaction

in cells in a manner analogous to that of a ligand. Likewise, an antagonist is defined herein as a compound that inhibits the function of a ligand or agonist toward the protein(s) of the invention and includes both natural and unnatural compounds.

5 In a method in which an intracellular biochemical change is used as an index, for example, the above-described cells stably expressing a protein of the invention may be exposed to a test sample in the presence of a ligand, and the above-described biochemical index, such as cAMP production, change of intracellular calcium concentration,  
10 or activation of protein kinase C, may be measured. If inhibition is seen in the biochemical index, the compound contained in the test sample is judged to be an antagonist of the protein of the present invention.

Alternatively, for example, the above cells stably expressing  
15 a protein of the invention may be directly exposed to a test sample, and a biochemical change as above described may be measured to isolate an agonist.

In a method in which the activity to inhibit the binding between a receptor protein of the invention and a ligand is used as an index,  
20 for example, phage display method may be used to isolate an agonist or antagonist. Phage display may be performed using, for example, the pSKAN Phagemid Display System (Catalogue #OB-15 18-00) according to the literature (Nicholas C. et al. Science 273:458 (1996)).

A compound obtained by the method of screening of the present  
25 invention may be applied as a medicine to humans or others mammals, such as mouse, rat, guinea pig, rabbit, chicken, cat, dog, sheep, porcine, bovine, monkey, sacred baboon, or chimpanzee, according to the standard procedures.

For instance, the compound may be administered orally, in the  
30 form of tablet, if necessary coated with sugar, capsule, elixir, or microcapsule, or may be parenterally administered, in the form of sterile solution in water or other pharmaceutically acceptable solution, or injection of suspension. A medicine may be prepared by, for example, mixing a substance having activity to bind to the  
35 protein of the present invention with a physiologically acceptable carrier, flavor, excipient, vehicle, preservative, stabilizer, or

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binder to a form a unit or dosage that is required by standard pharmaceutical procedures. The amount of active ingredient contained within the medicine may provide an appropriate dose within an indicated range.

5 Additives, for instance, binders such as gelatin, corn starch, tragacanth gum, or Arabia gum, excipients such as crystalline cellulose, swelling agents such as corn starch, gelatin, or alginic acid, lubricants such as magnesium stearate, sweeteners such as sucrose, lactose, or saccharine, or flavors such as peppermint, Gaultheria  
10 adenoithrix oil, or cherry may be mixed within the tablet or capsule. If the preparative unit form is a capsule, liquid carriers such as fatty oils may be included as well. Sterile compositions for injection may be prepared by using vehicles such as distilled water for injection according to a standard pharmaceutical procedures.

15 Aqueous solutions such as saline, or isotonic solutions containing glucose or other adjuvants such as D-sorbitol, D-mannose, D-mannitol, or sodium chloride may be used for injection. To increase solubility, alcohols such as ethanol, polyalcohols such as propylene glycol, or polyethylene glycol, or non-ionic detergents such as  
20 polysorbate 80<sup>TM</sup>, or HCO-50 may be appropriately added as an adjuvant.

Sesame oil or soybean oil may be used as oleaginous solution. Solubilizing agents such as benzyl-benzoate or benzyl alcohol may be added to increase solubility. Buffers such as phosphate buffer or sodium acetate buffer, pain-killers such as procaine chloride,  
25 stabilizers such as benzyl alcohol or phenol, or antioxidants may be mixed as well. Prepared solutions for injection may be packed in an appropriate ampoule.

The dose of the compound having the activity to bind to the protein of the invention may vary depending on symptom, but may be, in general,  
30 approximately 0.1 to 100 mg, preferably approximately 1.0 to 50 mg, and more preferably approximately 1.0 to 20 mg administered orally per day for adult (60 kg body weight).

In case of parenteral administration, a dose of, for example, approximately 0.01 to 30 mg, preferably approximately 0.1 to 20 mg,  
35 and more preferably approximately 0.1 to 10 mg may be injected intravenously per day for adult (60 kg body weight), although the

dose may vary depending on the recipient, target organ, symptom, or method. In case of other animals, a dose normalized by the dose per 60 kg body weight may be applied.

An antibody of the present invention may be obtained as a  
5 monoclonal or polyclonal antibody by conventional methods.

To produce an antibody that specifically binds to the protein of the invention, the protein may be used as an antigen to immunize animals according to a standard method. Immune cells are thus obtained, and fused with known parental cells by standard cell fusion methods.  
10 Fusion cells are then screened for cells producing antibodies using standard methods.

More specifically, a monoclonal or polyclonal antibody that specifically binds to the protein of the invention may be generated as follows:

15 For instance, a protein of the invention used as an antigen to obtain an antibody may be derived from many animal species, but preferably it is from a mammal such as a human, mouse, or rat, or more preferably from a human. A human-derived protein may be obtained from the nucleotide or amino acid sequences disclosed herein.

20 Any protein having a biological activity of the proteins described herein, or its partial peptide may be used as an antigen in the present invention. A partial peptide may be, for example, an amino (N)-terminal or carboxy (C)-terminal fragment of the protein. Herein, an antibody is defined as an antibody that specifically reacts  
25 with either the full length or a fragment of the protein.

A gene encoding a protein of the invention or its fragment may be inserted into a known expression vector, which is used to transform a host cell as described herein. The desired protein or its fragment may be recovered from the outside or inside of host cells, or from  
30 host cells by any standard method, and may be used as an antigen. Alternatively, cells expressing the protein or their lysates, or a chemically synthesized protein may be used as an antigen.

Any mammalian animal may be immunized with the antigen, but preferably the compatibility with parental cells used for cell fusion  
35 is taken into account. In general, animals of Rodentia, Lagomorpha, or Primates are used.

Animals of Rodentia include, for example, mouse, rat, and hamster. Animals of Lagomorpha include, for example, rabbit. Animals of Primates include, for example, a monkey of Catarrhini (old world monkey) such as *Macaca fascicularis*, rhesus monkey, sacred baboon, or chimpanzee.

Methods for immunizing animals with antigens are known in the art. For instance, intraperitoneal injection or subcutaneous injection of antigens is used as a standard method for immunization of mammals. More specifically, antigens may be diluted and suspended in an appropriate amount with phosphate buffered saline (PBS), physiological saline, etc. If desired, the antigen suspension may be mixed with an appropriate amount of a standard adjuvant, such as Freund's complete adjuvant, made into emulsion, and then administered to mammalian animals. Preferably, it is followed by several administrations of antigen mixed with an appropriately amount of Freund's incomplete adjuvant every 4 to 21 days. An appropriate carrier may also be used for immunization. After immunization as above, serum is examined for increase of the amount of desired antibodies by a standard method.

Polyclonal antibodies to the proteins of the present invention may be prepared by collecting blood from the immunized mammal examined for the increase of desired antibodies in the serum, and by separating serum from the blood by any conventional method. Polyclonal antibodies may be used as serum containing the polyclonal antibodies, or if necessary, a fraction containing the polyclonal antibodies may be isolated from the serum.

To prepare monoclonal antibodies, immune cells are collected from the mammal immunized with the antigen and checked for the increased level of desired antibodies in the serum as described above, and are subjected to cell fusion. The immune cells used for cell fusion are preferably obtained from spleen. The other parent cell which is fused with the above immune cell is preferably a mammalian myeloma cell, and more preferably a myeloma cell that has acquired a special feature that can be used for selection of fusion cells by drug.

Cell fusion of the above immune cell and myeloma cell may be performed by any standard method, such as those described in the

literature (Galfre G. and Milstein C. Methods Enzymol. 73:3-46 (1981)).

Resulting hybridomas obtained by the cell fusion may be selected by cultivating them in a standard selection medium, such as HAT medium (hypoxanthine, aminopterin, and thymidine containing medium). The cell culture is typically continued in the HAT medium for several days to several weeks, the time being sufficient to allow all the other cells, except desired hybridoma (non-fused cells), to die. Then, the standard limiting dilution is performed to screen and clone a hybridoma cell producing the desired antibody.

Besides the above method, in which a non-human animal is immunized with an antigen for preparing hybridoma, human lymphocytes such as that infected by EB virus may be immunized with a protein, protein expressing cells, or their lysates *in vitro*. Then, the immunized lymphocytes are fused with human-derived myeloma cells that is capable of indefinitely dividing, such as U266, to yield a hybridoma producing a desired human antibody, able to bind to the protein can be obtained (Unexamined Published Japanese Patent Application (JP-A) No. Sho 63-17688).

Furthermore, transgenic animals having a repertory of human antibody genes may be immunized with a protein, protein expressing cells, or their lysates as an antigen. Antibody producing cells are collected from the animals, and fused with myeloma cells to obtain hybridoma, from which human antibodies against the protein can be prepared (see WO92-03918, WO93-2227, WO94-02602, WO94-25585, WO96-33735, and WO96-34096).

Alternatively, an immune cell, such as an immunized lymphocyte, producing antibodies may be immortalized by an oncogene and used for preparing monoclonal antibodies.

Monoclonal antibodies thus obtained can be also be recombinantly prepared using conventional genetic engineering techniques (see, for example, Borrebaeck C.A.K. and Larrick J.W. Therapeutic Monoclonal Antibodies, published in the United Kingdom by MacMillan Publishers LTD (1990)). A DNA encoding an antibody may be cloned from an immune cell such as a hybridoma or an immunized lymphocyte producing the antibody, inserted into an appropriate vector, and introduced into host cells to prepare a recombinant antibody. The present invention

also provides recombinant antibodies prepared as described above.

An antibody of the present invention may be a fragment of an antibody or modified antibody, so long as it binds to one or more of the proteins of the invention. For instance, the antibody fragment  
5 may be Fab, F(ab')<sub>2</sub>, Fv, or single chain Fv (scFv), in which Fv fragments from H and L chains are ligated by an appropriate linker (Huston J.S. et al. Proc. Natl. Acad. Sci. U.S.A. 85:5879-5883 (1988)). More specifically, an antibody fragment may be generated by treating an antibody with an enzyme such as papain or pepsin. Alternatively, a  
10 gene encoding the antibody fragment may be constructed, inserted into an expression vector, and expressed in an appropriate host cell (see, for example, Co M.S. et al. J. Immunol. 152:2968-2976 (1994); Better M. and Horwitz A.H. Methods Enzymol. 178:476-496 (1989); Pluckthun A. and Skerra A. Methods Enzymol. 178:497-515 (1989); Lamoyi E. Methods  
15 Enzymol. 121:652-663 (1986); Rousseaux J. et al. Methods Enzymol. 121:663-669 (1986); Bird R.E. and Walker B.W. Trends Biotechnol. 9:132-137 (1991)).

An antibody may be modified by conjugation with a variety of molecules, such as polyethylene glycol (PEG). The present invention  
20 provides such modified antibodies. The modified antibody can be obtained by chemically modifying an antibody. These modification methods are conventional in the field.

Alternatively, an antibody of the present invention may be obtained as a chimeric antibody, between a variable region derived  
25 from nonhuman antibody and the constant region derived from human antibody, or as a humanized antibody, comprising the complementarity determining region (CDR) derived from nonhuman antibody, the framework region (FR) derived from human antibody, and the constant region. Such antibodies can be prepared by using known technology.

30 Obtained antibodies may be purified to homogeneity. The invention is not limited to one particular method for antibody separation and purification. Any standard method of protein separation and purification may be used. The concentration of the obtained antibody may be determined by measuring absorbance, by enzyme-linked  
35 immunosorbent assay (ELISA), etc.

ELISA, enzyme immunoassay (EIA), radioimmunoassay (RIA), and/or

immunofluorescence may be used to measure the antigen binding activity of the antibody of the invention. In ELISA, the antibody of the present invention is immobilized on a plate, protein of the invention is applied to the plate, and then a sample containing a desired antibody, such as culture supernatant of antibody producing cells or purified antibodies, is applied. Then, a secondary antibody, that recognizes the primary antibody and is labeled with an enzyme such as alkaline phosphatase, is applied, and the plate is incubated. After washing, an enzyme substrate, such as p-nitrophenyl phosphate, is added to the plate, and the absorbance is measured to evaluate the antigen binding activity of the sample. A fragment of the protein, such as a C-terminal or N-terminal fragment, may be used as a protein. BIAcore (Pharmacia) may be used to evaluate the activity of the antibody according to the present invention.

The above methods allow for the detection or measurement of the protein of the invention, by exposing the antibody of the invention to a sample assumed to contain the protein of the invention, and detecting or measuring the immune complex formed by the antibody and the protein.

Because the method of detection or measurement of the protein according to the invention can specifically detect or measure a protein, the method may be useful in a variety of experiments in which the protein is used.

The present invention also provides DNA of a length of 15 nucleotides or longer that hybridize with DNA having the nucleotide sequence of SEQ ID NOs: 1 to 3 or 24 to 27, or with DNA complementary to the DNA (complementary strand). Thus, the present invention provides probes that can selectively hybridize with a DNA encoding a protein of the invention, a DNA complementary to such a DNA, or a nucleotide or its derivative, such as antisense oligonucleotide, a ribozyme, etc.

The present invention comprises, for example, an antisense oligonucleotide that hybridizes with any portion of the nucleotide sequence of SEQ ID NOs: 1 to 3 and 24 to 27. The antisense oligonucleotide is preferably an antisense of a continuous sequence of a length of 15 nucleotides or longer within the nucleotide sequence





or the like, and prepared as a tablet, powder, granule, capsule, liposome capsule, injectable solution, liquid formulation, nose drops, freeze-dried agent, etc. The above may be achieved according to standard methods.

5 For treating patients, a derivative of an antisense oligonucleotide of the present invention may be, for example, directly applied to the affected area of a patient, or administered into blood vessels so as to finally reach the affected area. Moreover, the derivative may be encapsulated in antisense-encapsulating materials  
10 such as liposome, poly-L-lysine, lipid, cholesterol, lipofectin, or their derivative in order to increase durability and/or membrane permeability.

Dose of the derivative of the antisense oligonucleotide of the present invention may be appropriately adjusted depending on the  
15 patient's conditions, and a favorable amount such as 0.1 to 100 mg/kg, or more preferably 0.1 to 50 mg/kg may be administered.

As the antisense oligonucleotides of the present invention inhibit expression of the protein of the invention, it finds utility as an inhibitor of biological activity of the protein of the invention.  
20 An inhibitor of expression comprising the antisense oligonucleotide of the present invention is useful because it can inhibit the biological activity of the protein of the invention.

## 25 Brief Description of the Drawings

Figure 1 shows a comparison of the amino acid sequences among known human olfactory receptors and GTAR14-1 and GTAR14-2. Shadowed residues are shared by at least four proteins out of five. Dotted residues are matched in all five proteins. Abbreviations are as  
30 follows:

OLF1 for human olfactory receptor 1 (GenBank Accession# U56420); OLF2 for human olfactory receptor 2 (GenBank Accession# L35475); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421); 14-1 for GTAR14-1; and 14-2 for GTAR14-2 (pseudogene).

35 Figure 2 shows a comparison of the amino acid sequences among known human olfactory receptors and GTAR14-3. Shadowed residues are



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leukocytes.

The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

Figure 8 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR14-3 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: heart, 10: brain, 11: placenta, 12: lung, 13: liver, 14: skeletal muscle, 15: kidney, 16: pancreas, 17: spleen, 18: thymus, 19: prostate, 20: testis, 21: ovary, 22: small intestine, 23: colon, and 24: peripheral leukocytes.

The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

Figure 9 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR14-5 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: heart, 10: brain, 11: placenta, 12: lung, 13: liver, 14: skeletal muscle, 15: kidney, 16: pancreas, 17: spleen, 18: thymus, 19: prostate, 20: testis, 21: ovary, 22: small intestine, 23: colon, and 24: peripheral leukocytes.

The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

Figure 10 shows the nucleotide sequence of the full length GTAR14-1 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-1 cDNA is also indicated. The amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, and -V).

Figure 11 shows the nucleotide sequence of the full length GTAR14-1 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 10. The amino acid sequence encoded by the GTAR14-1 cDNA is also indicated. The amino acid sequences predicted to be a transmembrane domain are underlined (TM-VI and -VII).

Figure 12 shows the nucleotide sequence of the full length GTAR14-3 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-3 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, and -V).

Figure 13 shows the nucleotide sequence of the full length GTAR14-3 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 12. The amino acid sequence encoded by the GTAR14-3 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-VI and -VII).

Figure 14 shows the nucleotide sequence of the full length GTAR14-5 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-5 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, and -IV).

Figure 15 shows the nucleotide sequence of the full length GTAR14-5 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 14. The amino acid sequence encoded by the GTAR14-5 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-V, -VI, and -VII).

Figure 16 shows the nucleotide sequence of GTAR11-1 which was obtained by genomic PCR. The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 11-1-S2 primer, and 11-1-A3 primer, respectively.

Figure 17 shows the nucleotide sequence of GTAR11-2 which was obtained by genomic PCR. The positions of the primers used are

underlined. The right-directed and left-directed arrows indicate the positions of 11-2-S2 primer, and 11-2-A2 primer, respectively.

Figure 18 shows the nucleotide sequence of GTAR11-3 which was obtained by genomic PCR. The positions of primers used are underlined.

5 The right-directed and left-directed arrows indicate the positions of 11-3-S2 primer, and 11-3-A2 primer, respectively.

Figure 19 shows the nucleotide sequence of GTAR11-4 which was obtained by genomic PCR. The positions of the primers used are underlined. The right-directed and left-directed arrows indicate  
10 the positions of 11-4-S2 primer, and 11-4-A2 primer, respectively.

Figure 20 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR11-1 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

15 Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: brain, 10: heart, 11: kidney, 12: liver, 13: lung, 14: pancreas, 15: placenta, 16: skeletal muscle, 17: colon, 18: ovary, 19: peripheral leukocytes, 20: prostate, 21: small intestine, 22: spleen, 23: testis,  
20 and 24: thymus.

The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard  
25 cDNA as a template using a primer set for G3PDH.

Figure 21 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR11-2 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

30 Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: brain, 10: heart, 11: kidney, 12: liver, 13: lung, 14: pancreas, 15: placenta, 16: skeletal muscle, 17: colon, 18: ovary, 19: peripheral leukocytes, 20: prostate, 21: small intestine, 22: spleen, 23: testis,  
35 and 24: thymus.

The left lane of each panel shows the result of the positive

control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

5 Figure 22 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR11-3 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

10 Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: brain, 10: heart, 11: kidney, 12: liver, 13: lung, 14: pancreas, 15: placenta, 16: skeletal muscle, 17: colon, 18: ovary, 19: peripheral leukocytes, 20: prostate, 21: small intestine, 22: spleen, 23: testis, and 24: thymus.

15 The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

20 Figure 23 is a photograph showing the result of RT-PCR analysis of the gene expression pattern of GTAR11-4 in human tissues.

A: Human Fetal MTC Panel (Clontech #K1425-1), B: Human MTC Panel I (Clontech #K1420-1), C: Human MTC Panel II (Clontech #K1421-1).

25 Lanes 1: fetal brain, 2: fetal heart, 3: fetal kidney, 4: fetal liver, 5: fetal lung, 6: fetal muscle, 7: fetal spleen, 8: fetal thymus, 9: brain, 10: heart, 11: kidney, 12: liver, 13: lung, 14: pancreas, 15: placenta, 16: skeletal muscle, 17: colon, 18: ovary, 19: peripheral leukocytes, 20: prostate, 21: small intestine, 22: spleen, 23: testis, and 24: thymus.

30 The left lane of each panel shows the result of the positive control in which human genomic DNA was amplified as a template using the same primer set. The right lane of each panel shows the product of the control reaction in which G3PDH was amplified from a standard cDNA as a template using a primer set for G3PDH.

35 Figure 24 shows the nucleotide sequence of the GTAR11-1 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE.

The amino acid sequence encoded by the GTAR11-1 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

5 Figure 25 shows the nucleotide sequence of the GTAR11-2 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-2 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

10 Figure 26 shows the nucleotide sequence of the GTAR11-3 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-3 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

15 Figure 27 shows the nucleotide sequence of the GTAR11-4 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-4 cDNA is also indicated. Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

20 Figure 28 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-1. Shadowed residues are shared by at least three proteins out of four. Dotted residues are matched in all four proteins. The N residue of the [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and  
25 the D-R-Y sequence in the [M-A-Y-D-R-Y-L/V-A-I/V-C] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined. Abbreviations are as follows:

30 OLF1 for human olfactory receptor 1 (GenBank Accession# U56420); OLF2 for human olfactory receptor 2 (GenBank Accession# L35475); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421); and 11-1 for GTAR11-1.

35 Figure 29 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-2. Dotted residues are matched in all three proteins. The N residue of [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine



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residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined. Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421); and 11-2 for GTAR11-2.

Figure 30 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-3. Dotted residues are matched in all three proteins. The N residue of [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined. Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421); and 11-3 for GTAR11-3.

Figure 31 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-4. Dotted residues are matched in all three proteins. The N residue of [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined. Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421); and 11-4 for GTAR11-4.

#### Best Mode for Carrying Out the Invention

#### Example 1. Isolation and analysis of GTAR14 genes

(1) BLAST search



Figure 2 shows comparison of the amino acid sequences among known human OLF1, OLF2, and OLF3, and protein of the present invention, GTAR14-3.

Figure 3 shows comparison of the amino acid sequences among known human OLF1, OLF2, and OLF3, and proteins of the present invention, GTAR14-4 and GTAR14-5. The amino acid sequence of GTAR14-4 is artificially created by reading through the in frame stop codon.

(2) Isolation of the genes of GTAR14-1, GTAR14-3, and GTAR14-5 by genomic PCR

The sequence of BAC129 clone U85195 was analyzed for the presence of an exon that is broadly conserved in known OLF receptors at the amino acid sequence level, and the predicted exon was used to design primers as follows.

For amplification of GTAR14-1, GTAR14-1-S1 (5'-ATG GAC AGT CTA AAC CAA ACA AGA GTG-3'; SEQ ID NO: 7), GTAR14-1-S2 (5'-ATG GCA TTC TCA GCC ATT TAT ATG CTA-3'; SEQ ID NO: 8), and GTAR14-1-S3 (5'-GGG AAC ATT CTC ATC ATC ATT GCC ACA-3'; SEQ ID NO: 9) were used as sense primers, and GTAR14-1-A1 (5'-TTA TGT ATA TGA TTT CGT GAA AAA AAC-3'; SEQ ID NO: 10), GTAR14-1-A2 (5'-TAC CTC CTC ATT CCT CAA GGT GTA AAT-3'; SEQ ID NO: 11), and GTAR14-1-A3 (5'-GGT GAC CAC TGT GTA GAA GAC AGA CAC-3'; SEQ ID NO: 12) were used as antisense primers.

For amplification of GTAR14-3, GTAR14-3-S1 (5'-ATG GAA AGA ATC AAC AGC ACA CTG TTG-3'; SEQ ID NO: 13), and GTAR14-3-S2 (5'-TCT AAT CTA CAT CCT GAC TCA GCT GGG-3'; SEQ ID NO: 14) were used as sense primers, and GTAR14-3-A1 (5'-TTC AAA CCT CAC TCG GAG TTC TTG GGC-3'; SEQ ID NO: 15), and GTAR14-3-A2 (5'-AGC TTC ACC TCT TGG TTC CGC AGA GTG-3'; SEQ ID NO: 16) were used as antisense primers.

For amplification of GTAR14-5, GTAR14-5-S1 (5'-ATG GGA AAG ACC AAA AAC ACA TCG CTG-3'; SEQ ID NO: 17), and GTAR14-5-S2 (5'-CGT GGT GAC AGA TTT CAT TCT TCT GGG-3'; SEQ ID NO: 18) were used as sense primers, and GTAR14-5-A1 (5'-TCA ACC TGC TGT TAT CCT CTT CAG GGC-3'; SEQ ID NO: 19), and GTAR14-5-A2 (5'-CCT GGT TCC TCA GTG TAT AGA TGA GGG-3'; SEQ ID NO: 20) were used as antisense primers.

Genomic PCR was performed using Human Genomic DNA (Clontech #6550-1) as a template, and primer sets of "14-1-S1 and 14-1-A1," "14-1-S1 and 14-1-A2," "14-1-S2 and 14-1-A1," and "14-1-S2 and 14-1-A2"

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for amplification of GTAR14-1, "14-3-S1 and 14-3-A1," "14-3-S1 and 14-3-A2," "14-3-S2 and 14-3-A1," and "14-3-S2 and 14-3-A2" for amplification of GTAR14-3, and "14-5-S1 and 14-5-A1," "14-5-S1 and 14-5-A2," "14-5-S2 and 14-5-A1," and "14-5-S2 and 14-5-A2" for  
5 amplification of GTAR14-5. PCR was performed using the Advantage cDNA Polymerase Mix (Clontech #8417-1) on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400). By performing PCR under the following conditions, a single band was observed with a predicted size for each primer set.

10 PCR condition: 94°C for 4 min, 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C for 20 sec and 70°C for 2 min, 28 cycles of 94°C for 20 sec and 68°C for 2 min, 72°C for 4 min, and termination at 4°C.

The obtained products of genomic PCR were subcloned into the  
15 pGEM-T Easy vector (Promega #A1360), and the nucleotide sequence was determined. The PCR products were cloned into the pGEM-T Easy vector by ligation using T4 DNA ligase (Promega #A1360) at 4°C for 12 hr. The sample was used to transform *E. coli* DH5α (Toyobo # DNA-903) to obtain recombinants of the PCR products and the pGEM-T Easy vector.  
20 Recombinants were selected by using the Insert Check Ready (Toyobo #PIK-101). The nucleotide sequence was determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377).

Ten independent clones of recombinants were selected for each  
25 gene from the products of genomic PCR that had been performed using a set of primers that are located in the most external sites of the target gene fragment; that is, the product of the primer set of "14-1-S1 and 14-1-A1" for GTAR14-1 gene, that of "14-3-S1 and 14-3-A1" for GTAR14-3 gene, and that of "14-5-S1 and 14-5-A1" for GTAR14-5 gene.  
30 The complete nucleotide sequence of the inserts of all the clones were determined.

As a result, all clones of GTAR14-1 gene and GTAR14-3 gene showed a single nucleotide sequence of 942 bp. All clones of GTAR14-5 exhibited a single nucleotide sequence of 933 bp. The obtained  
35 sequences were verified to be a partial nucleotide sequence of respective genes and confirmed to not be a non-specific product of

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genomic PCR. Accordingly, these primer sets are expected to be able to work correctly in RT-PCR as described in the following (3). The partial nucleotide sequences of GTAR14-1, GTAR14-3, and GTAR14-5, obtained by genomic PCR, are shown in Figures 4, 5, and 6, and SEQ ID NO: 21, 22, and 23, respectively.

(3) Analysis of tissue distribution and patterns of GTAR14-1, GTAR14-3, and GTAR14-5 gene expressions by RT-PCR

For analysis of the tissue distribution and patterns of GTAR14-1, GTAR14-3, and GTAR14-5 gene expressions in human tissues, RT-PCR was performed using a primer set of "14-1-S2 and 14-1-A2," "14-3-S2 and 14-3-A2," and "14-5-S2 and 14-5-A2," respectively.

Human Fetal Multiple Tissue cDNA Panel (Clontech #K1425-1), Human Multiple Tissue cDNA Panel I (Clontech #K1420-1), and Human Multiple Tissue cDNA Panel II (Clontech #K1421-1) were used as a template. PCR was performed by using the Advantage cDNA Polymerase Mix (Clontech #8417-1) on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400). PCR reactions were performed under conditions with a single cycle of 94°C for 4 min, sequentially followed by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C for 20 sec and 70°C for 2 min, 38 cycles of 94°C for 20 sec and 68°C for 2 min, a single cycle of 72°C for 4 min, and termination at 4°C.

The result showed that a strong amplification of GTAR14-1 mRNA was observed only in thymus among human fetal tissues, and also in lymphatic/hematopoietic tissues including thymus and spleen, and testis and pancreas among adult tissues (Figure 7).

GTAR14-3 was strongly amplified in thymus, brain, heart, smooth muscle, and kidney among human fetal tissues, and weakly expressed in liver and lung as well. GTAR14-3 was strongly detected in thymus and testis among adult tissues, and also expressed in digestive organs such as small intestine and colon, and endocrine organs such as placenta and prostate, showing a broad distribution among tissues (Figure 8).

GTAR14-5 was strongly amplified in thymus, spleen, and lung among human fetal tissues, and weakly expressed in brain and kidney. It was detected strongly in lymphatic/hematopoietic tissues such as thymus, spleen, and peripheral leukocytes, and testis, and pancreas in adult tissues (Figure 9).

The products of PCR were subcloned into the pGEM-T Easy vector (Promega #A1360), and the nucleotide sequence were determined. The PCR products were cloned into the pGEM-T Easy vector by ligation using T4 DNA ligase (Promega #A1360) at 4°C for 12 hr. The samples were  
5 used to transform *E. coli* DH5α (Toyobo #DNA-903) to obtain recombinants of the PCR products and the pGEM-T Easy vector. Recombinants were selected by using the Insert Check Ready (Toyobo #PIK-101). The nucleotide sequence were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer  
10 (ABI PRISM 377). For each gene, ten independent recombinant clones were selected, and the complete nucleotide sequence of the inserts were determined. As a result, all clones showed a single nucleotide sequence.

The obtained sequences were verified to be a partial sequence  
15 of the GTAR14-1, GTAR14-3, or GTAR14-5, and confirmed not to be a non-specific product of RT-PCR.

(4) Full length cDNA cloning by 5'- and 3'-RACE

(i) 5'-RACE

5'-RACE-PCR was performed to isolate full length cDNAs of  
20 GTAR14-1, GTAR14-3, and GTAR14-5. Primers used for amplification of GTAR14-1, GTAR14-3, and GTAR14-5 genes were "14-1-A1," "14-3-A1," and "14-5-A1" for the first PCR, and "14-1-A2," "14-3-A2," and "14-5-A2" for the second PCR, respectively.

Human Testis Marathon-Ready cDNA Library (Clontech #7414-1) was  
25 used as a template, and the Advantage cDNA Polymerase Mix was used for PCR. PCR was performed on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400) under the following conditions:

first PCR: a single cycle of 94°C for 4 min, sequentially followed  
by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C  
30 for 20 sec and 70°C for 2 min, 30 cycles of 94°C for 20 sec and 68°C for 2 min, and a single cycle of 72°C for 4 min followed by termination at 4°C;

second PCR: a single cycle of 94°C for 4 min, sequentially followed  
by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 28 cycles of 94°C  
35 for 20 sec and 68°C for 2 min, and a single cycle of 72°C for 4 min followed by termination at 4°C.

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The obtained 5'-RACE-PCR products, which showed a single band, were subcloned into the pGEM-T Easy vector as described above. For six independent clones of recombinants, the nucleotide sequence of all inserts were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377), as described above.

(ii) 3'-RACE

3'-RACE-PCR was further performed to isolate full length cDNAs of GTAR14-1, GTAR14-3, and GTAR14-5 genes. Primers used for amplification of GTAR14-1, GTAR14-3, and GTAR14-5 genes were "14-1-S1," "14-3-S1," and "14-5-S1" for first PCR, and "14-1-S2," "14-3-S2," and "14-5-S2" for second PCR, respectively.

Again, Human Testis Marathon-Ready cDNA Library (Clontech #7414-1) was used as a template. PCR was performed using the Advantage cDNA Polymerase Mix under similar conditions to that for 5'-RACE-PCR described above, and PCR products of a single size were obtained. As described above, the obtained PCR products for respective genes were subcloned into the pGEM-T Easy vector. For six independent clones of recombinants, the nucleotide sequence of all inserts were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377). For each gene, all six independent clones showed a single nucleotide sequence. Finally, the nucleotide sequences obtained by 5'-RACE and 3'-RACE were combined to determine the nucleotide sequence of full length cDNA of GTAR14-1, GTAR14-3, and GTAR14-5. The determined nucleotide sequences of full length cDNAs are shown in Figures 10 and 11 (GTAR14-1), Figures 12 and 13 (GTAR14-3), and Figures 14 and 15 (GTAR14-5), and SEQ ID NO: 1 (GTAR14-1), SEQ ID NO: 2 (GTAR14-3), and SEQ ID NO: 3 (GTAR14-5).

Example 2. Isolation and analysis of GTAR11 genes

(1) BLAST search

When members of known olfactory receptor (OR) gene family are structurally compared one another, they are found to share a high homology in the second and seventh transmembrane domains at the amino acid sequence level. Accordingly, among these two domains, the

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present inventors chose a conserved amino acid sequence [LHTPMYFFLSNLSF] within the second transmembrane domain for query in BLAST search on the GenBank High Throughput Genomic Sequence (htgs) database, and tried to find a sequence of a novel useful gene belonging to the OR gene family. BLAST search was performed using default values of the TblastN (Ver.2.0.5) program. Besides detecting many sequences containing a known OR genes as a positive control, multiple human genomic sequences having a high structural homology to known OR genes were found. These sequences are found in a sequence of BAC clone originating from human chromosome 11 (GenBank Accession# AC002556), and show about 30 to 40% homology to known human olfactory receptor 1 (OLF1), OLF2, and OLF3 at the amino acid sequence level. Based on the results of analysis of gene expression pattern as described below and prediction of function, the four discovered genes were named G protein-coupled T-cell Activating Receptor 11-1 (GTAR11-1), G protein-coupled T-cell Activating Receptor 11-2 (GTAR11-2), G protein-coupled T-cell Activating Receptor 11-3 (GTAR11-3), and G protein-coupled T-cell Activating Receptor 11-4 (GTAR11-4), respectively.

## (2) Isolation of GTAR11 genes by genomic PCR

The sequence of the BAC clone AC002556 was analyzed for the presence of an exon that is broadly conserved in known OLF receptors at the amino acid sequence level, and the exon predicted was used to design primers as follows.

For amplification of GTAR11-1, GTAR11-1-S1 (5'-GAA GAG CAG TGA GGG TCC ATG TTA AGG-3'; SEQ ID NO: 34), and GTAR11-1-S2 (5'-CAG CAG CTT GTC CTT CGT CGA TTT CTG C-3'; SEQ ID NO: 35) were used as sense primers, and GTAR11-1-A2 (5'-GCT AGG GTG GGC ACC AAG GTG TTA AAC CC-3'; SEQ ID NO: 36), and GTAR11-1-A3 (5'-TGC AAA AGG ACA GTT TCA TCA TGG CAC-3'; SEQ ID NO: 37) were used as antisense primers.

For amplification of GTAR11-2, GTAR11-2-S1 (5'-CAA AGA ACT CAC CCA AAT TCC TAC AGC T-3'; SEQ ID NO: 38), and GTAR11-2-S2 (5'-CAT GGT AGG CAA CCT TGG CTT GAT CAC-3'; SEQ ID NO: 39) were used as sense primers, and GTAR11-2-A1 (5'-GTT TAT TAA ATC ACA CAT AAC ACC ATC TG-3'; SEQ ID NO: 40), and GTAR11-2-A2 (5'-CAG AGA CAG AGC AAT GAC ATG AGA GCT AC-3'; SEQ ID NO: 41) were used as antisense primers.



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For amplification of GTAR11-3, GTAR11-3-S1 (5'-CAA AGA ACT CAC CCA AAT TCC TAC AGC C-3'; SEQ ID NO: 42), and GTAR11-3-S2 (5'-CAT GGT AGG CAA CCT TGG CTT GAT CAT-3'; SEQ ID NO: 43) were used as sense primers, and GTAR11-3-A1 (5'-GTT TAT TAA ATC ACA CAT AAC ACC ATC TG-3'; SEQ ID NO: 44), and GTAR11-3-A2 (5'-CAG AGA CAG AGC AAT GAC ATG AGA GCT AC-3'; SEQ ID NO: 45) were used as antisense primers.

For amplification of GTAR11-4, GTAR11-4-S1 (5'-CCA GAC AGC TCG CCA AGA GAG AAT GAC-3'; SEQ ID NO: 46), and GTAR11-4-S2 (5'-CCT TTA TAG ATC TCT GTT ATT CCT GTG TG-3'; SEQ ID NO: 47) were used as sense primers, and GTAR11-4-A1 (5'-TCG GTT GCC AGT GAT ATG AAG AGA CCC-3'; SEQ ID NO: 48), and GTAR11-4-A2 (5'-GGC TTT GGA TCT GCC CTC TGC AGA AGG-3'; SEQ ID NO: 49) were used as antisense primers.

Genomic PCR was performed using Human Genomic DNA (Clontech #6550-1) as a template, and primer sets of "11-1-S1 and 11-1-A2," "11-1-S1 and 11-1-A3," "11-1-S2 and 11-1-A2," and "11-1-S2 and 11-1-A3" for amplification of GTAR11-1, "11-2-S1 and 11-2-A1," "11-2-S1 and 11-2-A2," "11-2-S2 and 11-2-A1," and "11-2-S2 and 11-2-A2" for amplification of GTAR11-2, "11-3-S1 and 11-3-A1," "11-3-S1 and 11-3-A2," "11-3-S2 and 11-3-A1," and "11-3-S2 and 11-3-A2" for amplification of GTAR11-3, and "11-4-S1 and 11-4-A1," "11-4-S1 and 11-4-A2," "11-4-S2 and 11-4-A1," and "11-4-S2 and 11-4-A2" for amplification of GTAR11-4. PCR was performed using the Advantage cDNA Polymerase Mix (Clontech #8417-1) on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400). Following conditions were used for PCR; a single cycle of 94°C for 4 min, sequentially followed by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C for 20 sec and 70°C for 2 min, 28 cycles of 94°C for 20 sec and 68°C for 2 min, and then a single cycle of 72°C for 4 min followed by termination at 4°C. As a result, a single band was detected with predicted size for each primer set.

The products obtained in the above genomic PCR were subcloned into the pGEM-T Easy vector (Promega #A1360), and the nucleotide sequence were determined. PCR products were cloned into the pGEM-T Easy vector by ligation using T4 DNA ligase (Promega #A1360) at 4°C for 12 hr. The samples were used to transform *E. coli* DH5α (Toyobo # DNA-903) to obtain recombinants of the PCR products and the pGEM-T

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Easy vector. Recombinants were selected by using the Insert Check Ready (Toyobo #PIK-101). The nucleotide sequences were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377).

5 For each gene, ten independent clones of recombinants were selected from the products of genomic PCR that had been performed using a set of primers that are located within the ORF of the target gene fragment; that is the product of the primer set of "11-1-S2 and 11-1-A3" for GTAR11-1 gene, that of "11-2-S2 and 11-2-A2" for GTAR11-2  
10 gene, that of "11-3-S2 and 11-3-A2" for GTAR11-3 gene, and that of "11-4-S2 and 11-4-A2" for GTAR11-4 gene. The nucleotide sequence of all the inserts were determined.

As a result, a single nucleotide sequence of 450 bp was obtained from all clones of GTAR11-1 gene. From all clones of GTAR11-2 and  
15 GTAR11-3 genes, a single nucleotide sequence of 637 bp was obtained. A single nucleotide sequence of 509 bp was obtained from all clones of GTAR11-4 gene. The obtained sequences were verified to be a partial nucleotide sequence of the respective genes to confirm that they are not a non-specific product of genomic PCR. Accordingly, these primer  
20 sets are expected to work correctly in RT-PCR described in the following (3). The partial nucleotide sequences of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 obtained by the genomic PCR are shown in Figures 16, 17, 18, and 19, and SEQ ID NO: 50, 51, 52, and 53, respectively.

(3) Analysis of tissue distribution and patterns of GTAR11 gene  
25 expressions by RT-PCR

For analysis of the tissue distribution and patterns of GTAR11 gene expressions in human tissues, RT-PCR was performed using a primer set of "11-1-S2 and 11-1-A2," "11-2-S2 and 11-2-A2," "11-3-S2 and 11-3-A2," and "11-4-S2 and 11-4-A2" for GTAR11-1, GTAR11-2, GTAR11-3,  
30 and GTAR11-4 genes, respectively.

Human Fetal Multiple Tissue cDNA Panel (Clontech #K1425-1), Human Multiple Tissue cDNA Panel I (Clontech #K1420-1), and Human Multiple Tissue cDNA Panel II (Clontech #K1421-1) were used as a template. PCR was performed by using the Advantage cDNA Polymerase Mix (Clontech  
35 #8417-1) on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400). PCR reactions were performed under conditions with a single cycle

of 94°C for 4 min, sequentially followed by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C for 20 sec and 70°C for 2 min, 38 cycles of 94°C for 20 sec and 68°C for 2 min, and then a single cycle of 72°C for 4 min followed by termination at 4°C.

5 The result showed a strong amplification of GTAR11-1 mRNA in spleen and weak expression in brain, lung, and smooth muscle among human fetal tissues. GTAR11-1 gene was also expressed in multiple tissues in adult including lymphatic/hematopoietic tissues such as thymus, spleen, and peripheral lymphocytes, digestive organs such  
10 as small intestine and colon, genital organs, neuronal tissues, and endocrine organs (Figure 20).

GTAR11-2 gene was strongly amplified in thymus, and weakly expressed in spleen, smooth muscle, lung, and kidney among fetal tissues. GTAR11-2 gene was also detected in multiple tissues in adult including  
15 lymphatic/hematopoietic tissues such as thymus and peripheral lymphocytes, digestive organs, genital organs, neuronal tissues, and endocrine organs (Figure 21).

GTAR11-3 gene was strongly amplified in smooth muscle among human fetal tissues, and weakly expressed in brain, lung, and liver as well.  
20 The gene was also detected in multiple tissues in adult including lymphatic/hematopoietic tissues such as thymus, spleen, and peripheral lymphocytes, digestive organs such as small intestine and colon, muscle, genital organs, neuronal tissues, and endocrine organs (Figure 22).

GTAR11-4 gene was strongly amplified only in smooth muscle in  
25 fetus. It was also expressed in multiple tissues in adult including lymphatic/hematopoietic tissues such as thymus, spleen, and peripheral lymphocytes, digestive organs such as small intestine and colon, muscle, genital organs, and endocrine organs (Figure 23).

The obtained PCR products were subcloned into the pGEM-T Easy  
30 vector (Promega #A1360), and the nucleotide sequence were determined. The PCR products were cloned into the pGEM-T Easy vector by ligation using T4 DNA ligase (Promega #A1360) at 4°C for 12 hr. The samples were used to transform *E. coli* DH5α (Toyobo # DNA-903) to obtain recombinants of the PCR products and the pGEM-T Easy vector.  
35 Recombinants were selected by using the Insert Check Ready (Toyobo #PIK-101). The nucleotide sequence were determined by using the

dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377). For each gene, ten independent clones of recombinants were selected, and the nucleotide sequence of all the inserts were determined. All clones of each gene showed a single nucleotide sequence.

The obtained sequences were verified to be a partial sequence of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 genes, and confirmed not to be a non-specific product of RT-PCR.

(4) Cloning of full length cDNA by 5'- and 3'-RACE

(i) 5'-RACE

To isolate full length cDNAs of GTAR11 genes, 5'-RACE-PCR was performed. Primers used for amplification of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 genes were "11-1-A2," "11-2-A1," "11-3-A1," and "11-4-A1" for first PCR, and "11-1-A3," "11-2-A2," "11-3-A2," and "11-4-A2" for second PCR, respectively.

Human Testis Marathon-Ready cDNA Library (Clontech #7414-1) was used as a template, and the Advantage cDNA Polymerase Mix was used for PCR. PCR was performed on a thermal cycler (Perkin Elmer Gene Amp PCR System 2400) under the following conditions:

first PCR: a single cycle of 94°C for 4 min, sequentially followed by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 5 cycles of 94°C for 20 sec and 70°C for 2 min, 30 cycles of 94°C for 20 sec and 68°C for 2 min, and a single cycle of 72°C for 4 min followed by termination at 4°C;

second PCR: a single cycle of 94°C for 4 min, sequentially followed by 5 cycles of 94°C for 20 sec and 72°C for 2 min, 28 cycles of 94°C for 20 sec and 68°C for 2 min, and a single cycle of 72°C for 4 min followed by termination at 4°C.

The obtained 5'-RACE-PCR products, detected as a single band, were subcloned into the pGEM-T Easy vector, six independent clones of recombinants were selected for each, and the nucleotide sequence of all inserts were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377), as described above.

(ii) 3'-RACE

3'-RACE-PCR was further performed to isolate full length cDNAs

of GTAR11 genes. Primers used for amplification of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 genes were "11-1-S1," "11-2-S1," "11-3-S1," and "11-4-S1" for first PCR, and "11-1-S2," "11-2-S2," "11-3-S2," and "11-4-S2" for second PCR, respectively.

Again, Human Testis Marathon-Ready cDNA Library (Clontech #7414-1) was used as a template. PCR was performed using the Advantage cDNA Polymerase Mix under similar conditions to that of 5'-RACE-PCR described above, and PCR products of a single size were obtained. As described above, the obtained products were subcloned into the pGEM-T Easy vector, six independent clones of recombinants were selected for each, and the nucleotide sequence of all inserts were determined by using the dRhodamine Terminator Cycle Sequencing kit (ABI/Perkin Elmer #4303141) on a DNA Sequencer (ABI PRISM 377). All six clones of each gene showed a single sequence. The nucleotide sequences obtained by 5'-RACE and 3'-RACE were combined to generate the sequence of full length cDNA of each GTAR11 gene. The resulting nucleotide sequences of cDNAs are shown in Figure 24 (GTAR11-1), Figure 25 (GTAR11-2), Figure 26 (GTAR11-3), and Figure 27 (GTAR11-4), and SEQ ID NO: 24 (GTAR11-1), SEQ ID NO: 25 (GTAR11-2), SEQ ID NO: 26 (GTAR11-3), and SEQ ID NO: 27 (GTAR11-4).

The GTAR11-1 cDNA obtained by the first 3'-RACE-PCR had a deletion at the C-terminus, and thus was not full length (the nucleotide sequence of the cDNA and the amino acid sequence of the peptide encoded by the cDNA are shown in SEQ ID NO: 32, and SEQ ID NO: 33, respectively). Consequently, 3'-RACE-PCR was performed again for GTAR11-1, and the full length cDNA of GTAR11-1 was obtained as described above.

The genome of known OR gene family shares a unique structural feature that the ORF from the initiation codon to the stop codon is contained in a single exon of the genome sequence encoding known OR genes. The isolated full length cDNAs of GTAR11-1, GTAR11-2, GTAR11-3, and GTAR11-4 genes also have their whole ORF within a sequence that is supposed to be a single exon.

Figure 28 shows comparison of the amino acid sequences of known human OLF1, OLF2, and OLF3, and GTAR11-1. Figure 29 shows comparison of the amino acid sequences of known human OLF2 and OLF3, and GTAR11-2. Figure 30 shows comparison of the amino acid sequences of known human

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OLF2 and OLF3, and GTAR11-3. Figure 31 shows comparison of the amino acid sequences of known human OLF2 and OLF3, and GTAR11-4.

Industrial Applicability

5           The present invention provides novel G protein-coupled receptor proteins and their genes. According to their particular expression patterns and such, the receptor proteins of the present invention appear to be involved in immune response, hematopoiesis, etc. Thus, one can use these proteins in screening assays, for developing drugs  
10       that can regulate immune response and/or hematopoietic cells. Using the receptor proteins of the present invention, one can also screen for ligands capable of binding to the receptor proteins of the invention, such ligands also being potentially involved in immune response, hematopoiesis, and so on.

15

# CLAIMS

1. A G protein-coupled receptor protein selected from the group consisting of:

5 (a) a protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 5, 6, 28, 29, 30, and 31;

(b) a protein of (a), wherein one or more amino acids are modified by deletion, addition, insertion, and/or substitution by another amino acid residue; and

10 (c) a protein encoded by DNA that hybridizes with DNA having a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 24, 25, 26, and 27.

2. A fusion protein comprising the protein of claim 1 and another peptide or polypeptide.

15 3. A peptide comprising a part of the protein of claim 1.

4. A DNA encoding the protein or peptide of any of claims 1 to 3.

5. A vector comprising the DNA of claim 4 inserted therein.

6. A transformant carrying the DNA of claim 4 in an expressible  
20 manner.

7. A method of producing the protein or peptide of any of claims 1 to 3, comprising the steps of: cultivating the transformant of claim 6, and recovering the protein or peptide expressed therein.

8. A method of screening for a compound that is capable of  
25 binding to the protein of claim 1, comprising the steps of:

(a) exposing a test sample to the protein or peptide of any of claims 1 to 3, and

(b) selecting the compound that binds to the protein or peptide of any of claims 1 to 3.

30 9. A method of screening for a ligand and/or agonist that is capable of binding to the protein of claim 1, comprising the steps of:

(a) exposing a test sample to a cell expressing the protein or peptide of any of claims 1 to 3 on its surface,

35 (b) measuring a biochemical change in said cell, and

(c) selecting the compound that induces said biochemical change





ABSTRACT

Partial cDNA sequences of target genes are obtained by performing RT-PCR with the use of an oligonucleotide primer designed based on a human genome sequence containing novel G protein-coupled receptor genes identified within a database. Further, full-length cDNAs of these genes are successfully isolated by the 5' -RACE method and 3' -RACE method, with the use of a human testis-origin cDNA library as a template. The proteins encoded by thus isolated genes have the characteristics of known olfactory receptor (OR) gene family. Moreover, the expression properties of them suggest that these genes may have functions relating to immune response and hemopoiesis.

SCANNED, #12

Figure 1

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OLF1 MEFTD-RNYT -LVTEFILLG FPTRPELQIV LFLMFLTYA IILIGNIQLM LLIRIDPHLQ
OLF2 M---D---NQS S-TPGFLLIG FSEHPGLGRT LFVDVITSYL LTLVGNTLTI LLSALDTKLIH
OLF3 MG-TD---NOT -WVSEFILLG LSSDWDRVS LEVLFLVMYV VTVLGNCLIV LLIRLDSRLH
14-1 M---DSLNOT -RVTEFVFLG LTDNRVLEML FEMAFSAIYM LTLSCNILLI IATVETPSLIH
14-2 MEEAILLNOT SLVTYFRLRG LSVNHKARIA MFSMFLIPYV LTLIGNVLIV ITIYDHRLIH
      *      *      *      *      *      *      *
OLF1 TPMYFFLSNL SEVDLCYFSD IVPKMLVNFL SENKSISYVG CALQYFFCT FADTESILLA
OLF2 SPMYFFLSNL SFDLDCFTTS CVPOMLANLW GERKTISELD CSVQIFIFLS LGTTECIEMK
OLF3 TPMYFFLTNL SLVDVSYATS VVPOLLAHFL AEHKAIPFOS CAAQLFTSLA LGGIEFVILA
14-1 TPMYFFLSNL SFIDICHSSV TVPKMLEGLL LERKTISPDN CITQLEFLHL FACAEIFILI
14-2 TPMYFFLSNL SFIDVCHSTV TVPKMLRDVW SEEKLISFDA CVTOMFFLHL FACTEIFILT
      ***** * * * * * * * * *
OLF1 AMAIDRYVAI CNPLLYTVVM SRGICMRLIV LSYLGGNMSS LVHTSFAFIL KYCDKNVINH
OLF2 VMAIDRYVAV CQPLHYATII HPRLCWQLAS VAWVIGLVGS VVQTPSTLHL PFCPDRQVDD
OLF3 VMAIDRYVAV CDALRYSAIM HGGLCARLAI TSWVSGFISS PVQTAITFQL PMCRNKFIDH
14-1 IVAIDRYVAI CTEPHYPNVM NMRVCIQLVF ALWLGGTVHS LGQFFLTIRL PYCGPNIIDS
14-2 VMAIDRYVAI CKPLQYMIVM NWKVCVLLAV ALWTGGTIHS IALTSLTIKL PYCGPDEIDN
      ** ***** * * * * * * * *
OLF1 FFCDLPLLLK LSCTDTTINE WLLSTYGSSV EIICFIIIII SYFFILLSVL KIRSFSGRKK
OLF2 FVCEVPALIR LSCEDTSYNE IQAVASVFI LUVPLSLILV SYGAIWAVL RINSATAWRK
OLF3 ISCELLAVVR LACVDTSNE VTIMVSSIVL LMTPLCLVLL SYIQIISTIL KIQSREGRKK
14-1 YFCDVPLVIK LACTDTYLTG ILIVTNSGTI SLSCFLAVVT SYMVIL-VSL RKHSAREGRK
14-2 FFCDVPPVIK LACIDTPTSL ILIVSNSGLI SVVCFVVLV SVAVIL-VSL ROQISGKWK
      *      * * * * *      * * * *
OLF1 TFSTCASHLT SVTIYQGTLL FIYSRPSYLY SPNTDKIISV FYTIFIPVLN PLIYSLANKD
OLF2 AFGTCSSHLT VVTLFYSSVI AVYLOKPNPY AQGRGRFEGF FYAVGTPLSN PLVYTLANKK
OLF3 AFHTCASHLT VVALCYGVAI FTYIQPHSSP SVLQEKLFVS FYAILTPMLN PMIYSLRNKE
14-1 ALSTCSAHEM VVALFFGPCI FIYTRPDTSF SI--DKVSV FYTVVTPLLN PFIYTLRNEE
14-2 ALSTCAAHLT VVTLFLGHCI FIYSRPSTSL PE--DKAVSV FETAVTPLLN PFIYTLRNEE
      *      *      *      *      *      *      *      *      *
OLF1 VKDAAEKVLR SKVDS--S
OLF2 IKRALRRLLG KERDSRESWR AA
OLF3 VKGAWQKLLW KFSG-LTSKL AT
14-1 VKSAMQQLRQ RQVF-FT-KS YT
14-2 MKSALNKLVG RK-E-R--KE EK
      *      *

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Figure 2

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OLF1 MEFTD-RNYT LVTEFILLGF PTRPELOIVL FEMFLTLYAI ILIGNIGIME LIRIDPHLO-
OLF2 M---D---MOS STPGFILLGF SEHPGLGRTL FVDVITSYLL TLVGNTEIIL LSALDTKLEH-
OLF3 MG-TD---NQT WVSEFILLGL SSDWDTRVSL FVLFLVMYVV TVLGNCLIVL LIRLDSREH-
14-3 ME-RI---NST LLTAFILTGI PYPLRLRTLE FVFFFLIYIL TOLGNLEILI TVWADPRLHA
      *      *      *      *      *      *      *      *
OLF1 TPMYFFLSNL SFVDLCYFSD IVEKMLVNEL SENKSISYVG CALQFYFFCT FADTESFILA
OLF2 SPMYFFLSNL SFDLCTTS CVPOMLANLW GPKKTISFLD CSVOIFIFLS LGTTECILMK
OLF3 TPMYFFLTNL SLVDVSYATS VVPQLLAHFL AEHKAIPFQS CAAQLFFSLA LGGTEFVLLA
14-3 RPYIIFLGVL SVIDMSISSI IVPRLMMFT LGVKPIPPGG CVAQLYFYHF LGSTQCFLYT
      *** * * * *      * *      * *      * *
OLF1 AMAYDRYVAI CNPLLYTVVM SRGICMLIV LSYLGGNMSS LVHTSFAPIL KYCDKNVINH
OLF2 VMAYDRYVAV COPLHYATIL HPRLCWOLAS VAWVIGLVGS VVQTPSTLHL PFCPDRQVDD
OLF3 VMAYDRYVAV CDALRYSAIM HGGLCARLAI TSWVSGFISS PVQTAITFOL PMCRNKFIDH
14-3 IMAYDRYLAI COPLRYPVLM TAKLSALLVA GAWMAGSIHG ALQAILTFRL PYCGPNQVDY
      ** * * * *      *      *      *      *
OLF1 FFCDLPELLK LSCTDTTINE WLLSTYGSSV EIICFIIIII SYFFILLSVL KIRSFSGRKK
OLF2 FVCEVPALIR LSCEDTSYNE IQVAVASVFI LVVPLSLILV SYGAIWAVE RINSATAWRK
OLF3 ISCELLAVVR LACVDTSSNE VTIMVSSIVL LMTPLCLVLL SYIQIISTIL KIQSREGRKK
14-3 FFCDIPAVLR LACADTTVNE LVTFVDIGVV VASCFSLLIL SYIQIIQAIL RIHTADGRRR
      *      * * * * *      * *      * *
OLF1 TFSTCASHLT SVTIYQGTLL FIYSRPSYLY SPNTDKIISV FYTIFIPVLN PLIYSLRNKD
OLF2 AFGTCSSHLT VVTLFYSSVI AVYLOPKNPY AQGRGKFFGL FYAVGTPSLN PLVYTLRNKE
OLF3 AFHTCASHLT VVALCYGVAI FTYIQPHSSP SVLQEKLFVS FYAILTPMLN PMIYSLRNKE
14-3 AFSTCGAEVT VVTIVYVPCA PIYLRPETNS PLD-GAAALV PTAI-TPPLN PLIYTLRNOE
      * * * * *      * *      * * * * *
OLF1 VKDAAEKVL- -RSKVDSS
OLF2 IKRALRRILG KERDSRESWR AA
OLF3 VKGAWOKLLW KFSGL-TSKL AT
14-3 VKLAL-KRM- LRSRTPSEV
      * *      *

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Figure 3

OLF1 MEFTD-RNYT -LVTEFILLG FPTRPELOIV LEFMPLTLYA IILIGNIGLM LLIRIDPHLO  
 OLF2 M---DMQS-- S-TPGFILLG FSEHPGLGRT LEVDVITSYL LTLVGNLTII LLSALDTKLH  
 OLF3 MG-TUMOT-- -WVSEFILLG LSSDWDTVS LEVLELVMYV VTVLGNCLIV LLIRLDSRLH  
 14-4 MGKTKNTSLD TVVRDFILLG LSHPPNIRSL LFLVEFVIYI LTOLGNLLIL LTVWADPKLR  
 14-5 MGKTKNTSLD AVVTDFILLG LSHPPNIRSL LFLVEFVIYI LTOLGNLLIL LTMWADPKLC  
 \* \* \* \* \* \*\* \* \* \* \*  
 OLF1 T-PMYFFLSN LSFVPLCYFS DIVPKMLVNF LSENKSISY GCALQFYFC TFADTESFIL  
 OLF2 S-PMYFFLSN LSFVPLCYFS DIVPKMLVNF LSENKSISY GCALQFYFC TFADTESFIL  
 OLF3 T-PMYFFLTN LSLVDVSYAT SVVQOLLAHF LAEHKAIPFO SCARQLEFSL ALGGIEFVLL  
 14-4 ARPMYILLGV LSFVDMWLS VIVE\*IILNF TPANKAIPFG GCVAQLYFFH FLGSTOCLY  
 14-5 ARPMYILLGV LSFVDMWLS VIVPRLLILDF TPSIKAIPFG GCVAQLYFFH FLGSTOCLY  
 \*\*\* \* \* \* \* \*\* \* \* \* \*  
 OLF1 AAMAYDRIVA ICNPLLYTVV MSRGICMLI VLSYLGGNMS SLVHTSFAFI LKYCDKNVIN  
 OLF2 KVMAYDRIVA VCQPLHYATI IHPRLCWOHA SVANVIGLVG SVVQTPSTLH LPFCPDROVD  
 OLF3 AVMAYDRIVA VCDALRYSAI MHGGLCARLA ITSWSGFIS SPVQTAITFO LPMCRNKFID  
 14-4 TLMAYDRILA ICQPLRYVVL MNGRLCTVLV AGAWVAGSMH GSIQATLTER LPYCGPNQVD  
 14-5 TLMAYDRILA ICQPLHYVVL MNGRLCTVLV AGAWVAGSMH GSIQATLTER LPYCGPNQVD  
 \*\*\* \* \* \* \* \* \* \* \* \*  
 OLF1 HFFCDLPPIL KLSCTDTIN EWLLSTYGSS VEIICFIIII ISYFFILLSV LKIRSFSGRK  
 OLF2 DFVCEVPALI RLSCEDTSYN EIQVAVASVF ILVVPLSLIL VSYGAIWAV LRINSATAMR  
 OLF3 HISCELLAVV RLACVDTSSN ERTIMVSSIV LLMTPLCLVL LSYIQIIST LKIQSREGRK  
 14-4 YFICDIPAVL RLACADTTVN ELVTFVDIGV VAASCEMLIL LSYANIVNAI LKIRTADGRR  
 14-5 YFICDIRAVL RLACADTTVN ELVTFVDVRV VAASCEMLIL LSYANIVNAI LKIRTADGRR  
 \* \* \* \* \* \* \* \* \* \*  
 OLF1 KTFSTCASHL TSVTIYQGTI LFIYSRPSYL YSPNTDKIIS VFYTIFFIVL NPLIYSLRNK  
 OLF2 KAFGTCCSHL TVVTLYSSV IAVYLOPKNP YAGRGKFFG LFYAVGTPSL NPLVYTLRNK  
 OLF3 KAFHTCASHL TVVALCYGVA IFYIOPHSS PSVLQEKLF VFYAILTPML NPMIYSLRNK  
 14-4 RAFSTCGSHL IVTVVYVPC IFIYLRAGSK G-PLDG-AAA VFYTVVTPLL NPLIYTLRNQ  
 14-5 RAFSTCGSHL IVTVVYVPC IFIYLRAGSK D-PLDG-AAA VFYTVVTPLL NPLIYTLRNQ  
 \* \* \* \* \* \* \* \* \* \*  
 OLF1 DVKDAAEKVLR SKVDS--S  
 OLF2 EIKRALRRLLG KERDSRESWR AA  
 OLF3 EVKGAWOKLLW KFSG-LTSKL AT  
 14-4 EVKSAL-KRI- -TAGQTE  
 14-5 EVKSAL-KRI- -TAG  
 \* \*

Figure 4

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1  ATGGACAGTC TAAACCAAAC AAGAGTGACT GAATTTGTCT TCTTGGGACT
51  CACTGATAAC CGGGTGCTGG AAATGCTGTT TTTCATGGCA TTCTCAGCCA
101 TTTATATGCT AACGCTTTCA GGAACATTC TCATCATCAT TGCCACAGTC
151 TTTACTCCAA GTCTCCATAC CCCCATGTAT TTCTTCCTGA GCAATCTGTC
201 CTTTATTGAC ATCTGCCACT CATCTGTCAC TGTGCCTAAG ATGTTGGAGG
251 GTTTGCTTTT AGAAAGAAAG ACCATTTCTT TTGACAACTG CATCACACAG
301 CTCTTCTTCC TACATCTCTT TGCCTGTGCC GAGATCTTTC TGCTGATCAT
351 TGTGGCGTAT GATCGTTACG TGGCTATCTG CACTCCACTC CACTACCCCA
401 ATGTGATGAA CATGAGAGTC TGTATACAGC TTGTCTTTGC TCTCTGGTTG
451 GGGGGTACTG TTCACTCACT AGGGCAGACC TTCTTGACTA TTCGTCTACC
501 TTAATGTGGC CCCAACATTA TTGACAGCTA CTTCTGTGAT GTGCCTCTTG
551 TTATCAAGCT GGCCTGCACA GATACATACC TCACAGGAAT ACTGATTGTG
601 ACCAATAGTG GAACCATCTC CCTCTCCTGT TTCTTGGCCG TGGTCACCTC
651 CTATATGGTC ATCCTGGTTT CTCTTCGAAA AACTCAGCT GAAGGGCGCC
701 AGAAAGCCCT GTCTACCTGC TCGGCCCACT TCATGGTGGT TGCCCTCTTC
751 TTTGGGCCAT GTATCTTCAT CTATACTCGG CCAGACACCA GCTTCTCCAT
801 TGACAAGGTG GTGTCTGTCT TCTACACAGT GGTCAACCCT TTGCTGAATC
851 CCTTCATTTA CACCTTGAGG AATGAGGAGG TAAAAAGTGC CATGAAGCAG
901 CTCAGGCAGA GACAAGTTTT TTTCACGAAA TCATATACAT AA

```

Figure 5

1    ATGGAAAGAA TCAACAGCAC ACTGTTGACT GCGTTTATCC TGACAGGAAT  
51    TCCGTATCCA CTCAGGCTAA GGACACTCTT TTTTGTGTTC TTTTTCCTAA  
101   TCTACATCCT GACTCAGCTG GGAAACCTGC TTATTTTAAT CACTGTCTGG  
151   GCAGACCCAA GGCTCCATGC CCGCCCCATG TACATCTTTC TTGGTGTCT  
201   CTCAGTCATT GATATGAGCA TCTCCTCCAT CATTGTCCCT CGCCTCATGA  
251   TGAACTTCAC TTTAGGTGTC AAACCCATCC CATTTGGTGG CTGTGTTGCT  
301   CAACTCTATT TCTATCACTT CCTGGGCAGC ACCCAGTGCT TCCTCTACAC  
351   CCTAATGGCC TATGACAGGT ACCTGGCAAT ATGTCAGCCC CTGCGCTACC  
401   CTGTGCTCAT GACTGCTAAG CTGAGCGCCT TGCTTGTGGC TGGAGCCTGG  
451   ATGGCAGGAT CCATCCATGG GGCTCTCCAG GCCATCCTAA CCTTCCGCCT  
501   GCCCTACTGT GGGCCCAATC AGGTGGATTA CTTCTTCTGT GACATCCCTG  
551   CAGTGTTGAG ACTGGCCTGT GCTGACACAA CAGTCAACGA GCTGGTGACG  
601   TTTGTAGACA TTGGGGTGGT GGTTGCCAGT TGCTTCTCCC TGATCCTCCT  
651   CTCCTACATA CAGATCATTC AGGCCATCCT GAGAATCCAC ACAGCTGATG  
701   GGCGGCGCCG GGCTTTTTC AACTTGTGGAG CCCATGTAAC CGTGGTCACC  
751   GTGTACTATG TGCCCTGTGC CTTATCTAC CTGAGGCCTG AAACCAACAG  
801   CCCCCTGGAT GGGGCAGCTG CCCTAGTCCC CACGGCCATC ACTCCTTTCC  
851   TCAACCCCTT TATCTACACT CTGCGGAACC AAGAGGTGAA GCTGGCCCTG  
901   AAAAGAATGC TCAGAAGCCC AAGAACTCCG AGTGAGGTTT GA

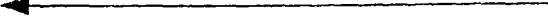


Figure 6

1    ATGGGAAAGA CAAAAACAC ATCGCTGGAT GCCGTGGTGA CAGATTTTCA  
51    TCTTCTGGGT TTGTCTCACC CCCCAAATCT AAGAAGCCTC CTCTTCCTGG  
101   TCTTCTTCAT CATTTACATC CTCACTCAGC TGGGGAACCT GCTCATTCTG  
151   CTCACCATGT GGGCTGACCC GAAGCTCTGT GCTCGCCCCA TGTACATTCT  
201   TCTGGGAGTG CTCTCATTCC TGGACATGTG GCTCTCCTCA GTCACCGTTC  
251   CTCGGCTTAT TTTGGATTTT ACTCCTTCCA TCAAGGCTAT CCCGTTTGGT  
301   GGCTGTGTGG CTCAACTGTA TTTCTTTTAC TTCCTGGGCA GCACCCAGTG  
351   CTCCTCTAC ACCTTGATGG CCTATGACAG GTACCTAGCA ATATGTCAGC  
401   CCCTGCACTA CCCAGTGCTC ATGAATGGGA GGTATGCAC AGTCCTTGTTG  
451   GCTGGAGCTT GGGTCGCCGG CTCCATGCAT GGGTCTATCC AGGCCACCTT  
501   GACCTTCCGC CTGCCCTACT GTGGGCCCAA TCAGGTGGAT TACTTTATCT  
551   GTGACATCCG CGCAGTATTG AGACTGGCCT GTGCTGACAC AACTGTCAAT  
601   GAGCTTGTGA CCTTTGTGGA CGTCAGGGTA GTGGCCGCCA GTTGCTTCAT  
651   GTTAATTCTG CTCTCCTATG CCAACATAGT CCATGCCATC CTGAAGATAC  
701   GCACCGCTGA TGGGAGGCGC CGGGCCTTCT CCACCTGTGG CTCCCACCTA  
751   ATCGTGGTCA CAGTCTACTA TGTCCCCTGT ATTTTCATCT ACCTTAGGGC  
801   TGGCTCCAAA GACCCCCTGG ATGGGGCAGC GGCTGTGTTT TACACTGTTG  
851   TCACTCCATT ACTGAACCCC CTCATCTATA CACTGAGGAA CCAGGAAGTG  
901   AAGTCTGCCC TGAAGAGGAT AACAGCAGGT TGA

Figure 7

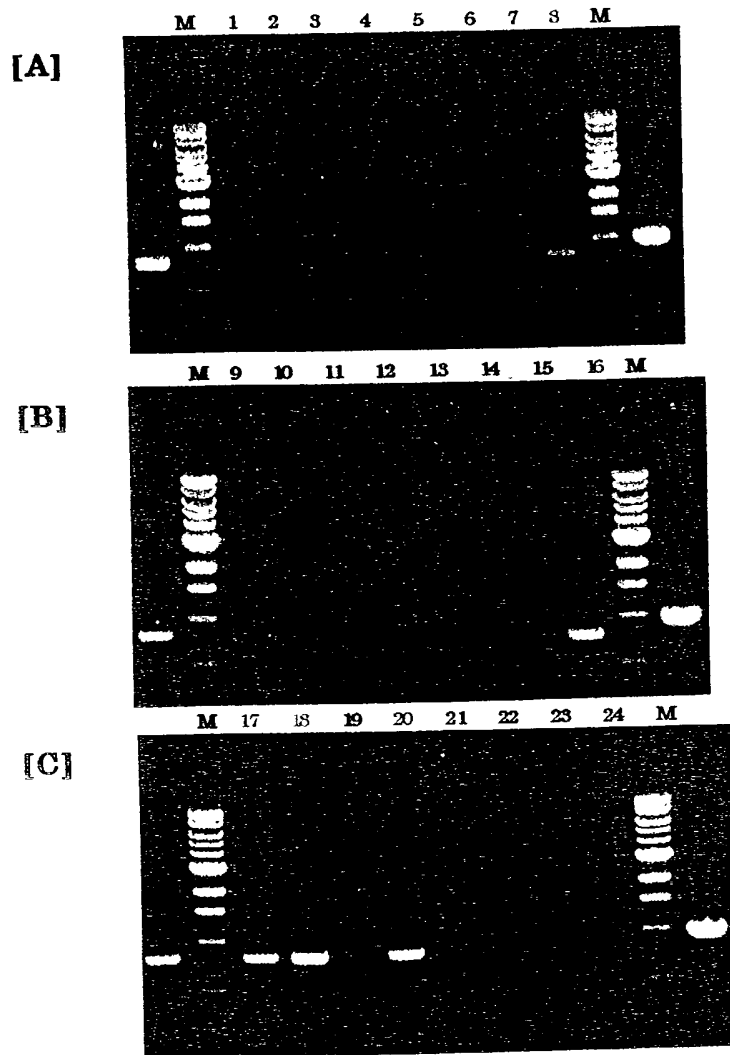




Figure 8

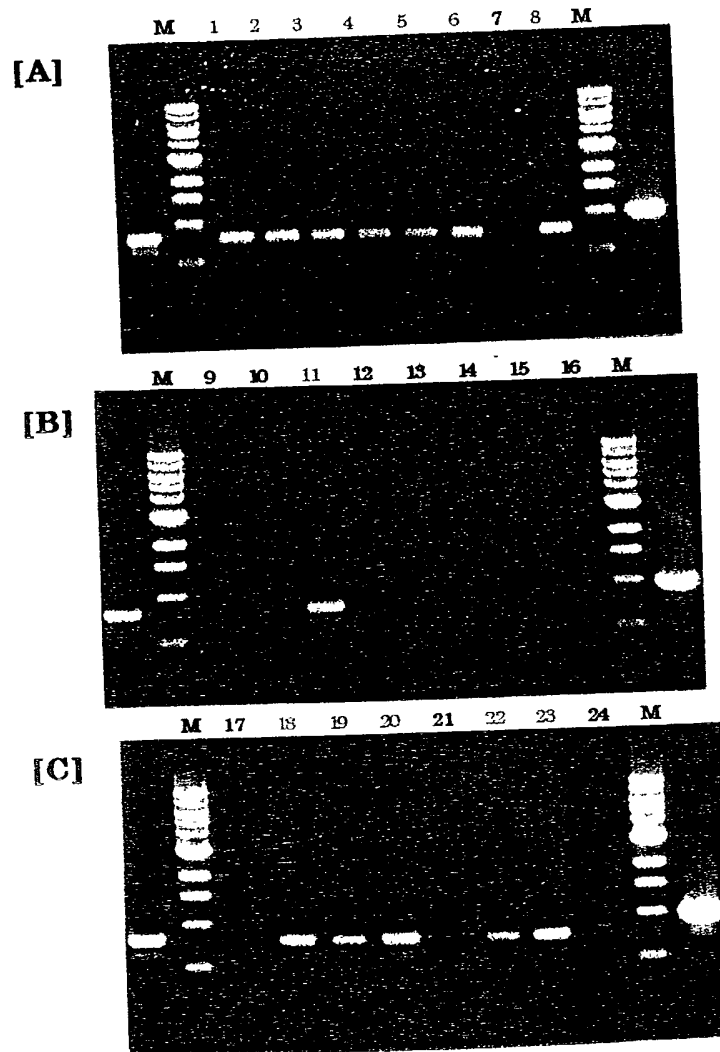


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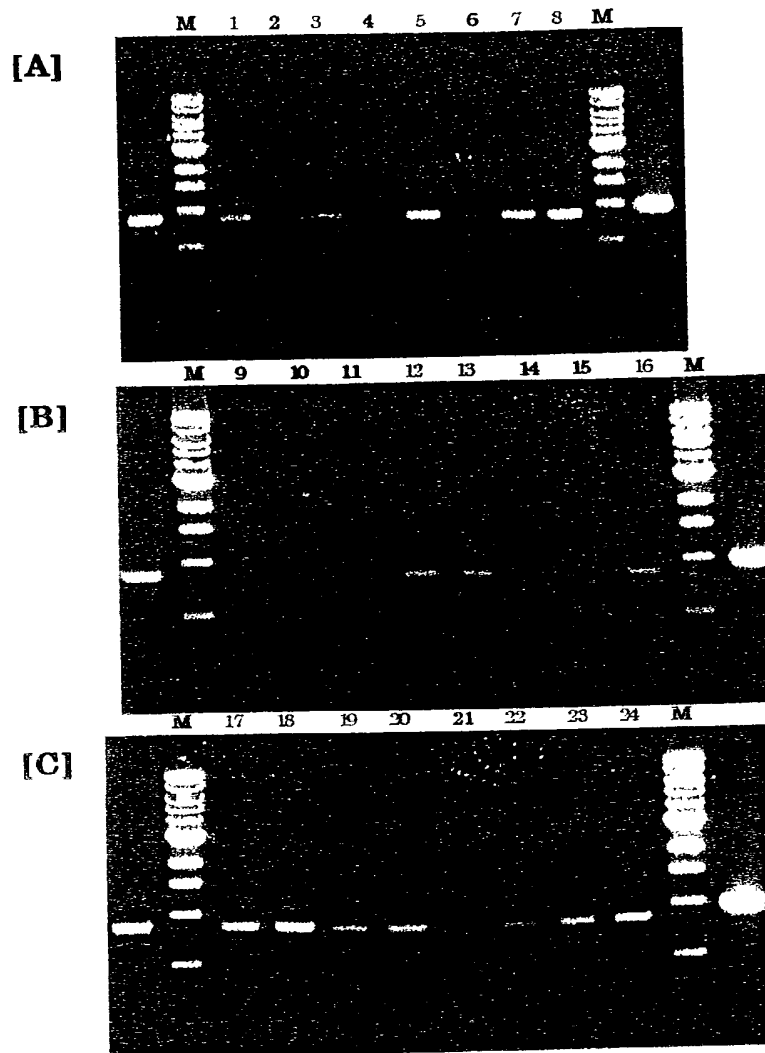


Figure 10

1 CTCATTGAATGGACAGTCTAAACCAAACAAGAGTGACTGAATTTGTCTTCTGGGACTCA  
MetAspSerLeuAsnGlnThrArgValThrGluPheValPheLeuGlyLeuThr

61 CTGATAACCGGGTGCTGGAAATGCTGTTTTTCATGGCATTCTCAGCCATTATATGCTAA  
AspAsnArgValLeuGluMetLeuPhePheMetAlaPheSerAlaIleTyrMetLeuThr  
TM-I

121 CGCTTTCAGGGAACATTCTCATCATCATTGCCACAGTCTTTACTCCAAGTCTCCATACCC  
LeuSerGlyAsnIleLeuIleIleIleAlaThrValPheThrProSerLeuHisThrPro

181 CCATGTATTTCTTCTGAGCAATCTGTCCTTTATTGACATCTGCCACTCATCTGTCACTG  
MetTyrPhePheLeuSerAsnLeuSerPheIleAspIleCysHisSerSerValThrVal  
TM-II

241 TGCCTAAGATGTTGGAGGGTTTGCTTTTAGAAAGAAAGACCATTTCCTTTGACAAC TGCA  
ProLysMetLeuGluGlyLeuLeuLeuGluArgLysThrIleSerPheAspAsnCysIle

301 TCACACAGCTCTTCTTCCTACATCTCTTGCCTGTGCCGAGATCTTCTGCTGATCATTG  
ThrGlnLeuPhePheLeuHisLeuPheAlaCysAlaGluIlePheLeuLeuIleIleVal  
TM-III

361 TGGCGTATGATCGTTACGTGGCTATCTGCACTCCACTCCACTACCCCAATGTGATGAACA  
AlaTyrAspArgTyrValAlaIleCysThrProLeuHisTyrProAsnValMetAsnMet

421 TGAGAGTCTGTATACAGCTTGTCTTTGCTCTCTGGTTGGGGGTACTGTTCACTCACTAG  
ArgValCysIleGlnLeuValPheAlaLeuTrpLeuGlyGlyThrValHisSerLeuGly  
TM-IV

481 GGCAGACCTTCTTGACTATTCTGCTACCTACTGTGGCCCCAACATTATTGACAGCTACT  
GlnThrPheLeuThrIleArgLeuProTyrCysGlyProAsnIleIleAspSerTyrPhe

541 TCTGTGATGTGCCTCTTGTTATCAAGCTGGCCTGCACAGATACATACCTCACAGGAATAC  
CysAspValProLeuValIleLysLeuAlaCysThrAspThrTyrLeuThrGlyIleLeu

601 TGATTGTGACCAATAGTGAACCATCTCCCTCTCCTGTTTCTTGCCGTGGTCACCTCCT  
IleValThrAsnSerGlyThrIleSerLeuSerCysPheLeuAlaValValThrSerTyr  
TM-V

661 ATATGGTCATCCTGGTTTCTCTTCGAAAACACTCAGCTGAAGGGCGCCAGAAAGCCCTGT  
MetValIleLeuValSerLeuArgLysHisSerAlaGluGlyArgGlnLysAlaLeuSer

Figure 11

721 CTACCTGCTCGGCCCACTTCATGGTGGTTGCCCTCTTCTTTGGGCCATGTATCTTCATCT  
ThrCysSerAlaHisPheMetValValAlaLeuPhePheGlyProCysIlePheIleTyr  
TM-VI  
781 ATACTCGGCCAGACACCAGCTTCTCCATTGACAAGGTGGTGTCTGTCTTCTACACAGTGG  
ThrArgProAspThrSerPheSerIleAspLysValValSerValPheTyrThrValVal  
841 TCACCCCTTTGCTGAATCCCTTCATTTACACCTTGAGGAATGAGGAGGTAAAAAGTGCCA  
ThrProLeuLeuAsnProPheIleTyrThrLeuArgAsnGluGluValLysSerAlaMet  
TM-VII  
901 TGAAGCAGCTCAGGCAGAGACAAGTTTTTTTACGAAATCATATACATAATGGGCATTGG  
LysGlnLeuArgGlnArgGlnValPhePheThrLysSerTyrThr\*\*\*  
961 GATTGCAGACATAATTGCAGCCACATCCTTAATGAAAGAGCAAAAGTAAAGAGTCAAAAT  
1021 CAACTTATATAACTTGGTAAATTAGGTAAAATGGCATAGAGCAGGTCAGATTTCTGCTCA  
1081 TTAAAGATAAGAACTTATTCTGTTCATTAAAGATAAGAACTTATTAAGTATTATTTAAAT  
1141 AAA

Figure 12

1 ATTCTCTGGGATATGGAAAGAATCAACAGCACACTGTTGACTGCGTTTATCCTGACAGGA  
MetGluArgIleAsnSerThrLeuLeuThrAlaPheIleLeuThrGly  
61 ATTCGGTATCCACTCAGGCTAAGGACACTCTTTTTTGTGTTCTTTTTTCTAATCTACATC  
IleProTyrProLeuArgLeuArgThrLeuPhePheValPhePhePheLeuIleTyrIle  
121 CTGACTCAGCTGGGAAACCTGCTTATTTTAATCACTGTCTGGGCAGACCCAAGGCTCCAT  
LeuThrGlnLeuGlyAsnLeuLeuIleLeuIleThrValTrpAlaAspProArgLeuHis  
TM-I  
181 GCGCGCCCATGTACATCTTTCTTGGTGTCTCTCAGTCATTGATATGAGCATCTCCTCC  
AlaArgProMetTyrIlePheLeuGlyValLeuSerValIleAspMetSerIleSerSer  
TM-II  
241 ATCATTGTCCCTCGCCTCATGATGAACTTCACTTTAGGTGTCAAACCCATCCCATTGGT  
IleIleValProArgLeuMetMetAsnPheThrLeuGlyValLysProIleProPheGly  
301 GGCTGTGTGCTCAACTCTATTTCTATCACTTCTGCGCAGCACCCAGTGCTTCTCTAC  
GlyCysValAlaGlnLeuTyrPheTyrHisPheLeuGlySerThrGlnCysPheLeuTyr  
TM-III  
361 ACCCTAATGGCCTATGACAGGTACCTGGCAATATGTGAGCCCTGCGCTACCCTGTGCTC  
ThrLeuMetAlaTyrAspArgTyrLeuAlaIleCysGlnProLeuArgTyrProValLeu  
421 ATGACTGCTAAGCTGAGCGCCTTGCTTGTGGCTGGAGCCTGGATGGCAGGATCCATCCAT  
MetThrAlaLysLeuSerAlaLeuLeuValAlaGlyAlaTrpMetAlaGlySerIleHis  
TM-IV  
481 GGGGCTCTCCAGGCCATCCTAACCTTCCGCTGCCCTACTGTGGGCCCCAATCAGGTGGAT  
GlyAlaLeuGlnAlaIleLeuThrPheArgLeuProTyrCysGlyProAsnGlnValAsp  
541 TACTTCTTCTGTGACATCCCTGCAGTGTGAGACTGGCCTGTGCTGACACAACAGTCAAC  
TyrPhePheCysAspIleProAlaValLeuArgLeuAlaCysAlaAspThrThrValAsn  
601 GAGCTGGTGACGTTTGTAGACATTGGGGTGGTGGTGGCAGTTGCTTCTCCCTGATCCTC  
GluLeuValThrPheValAspIleGlyValValValAlaSerCysPheSerLeuIleLeu  
TM-V  
661 CTCTCCTACATACAGATCATTGAGCCATCCTGAGAATCCACACAGCTGATGGGCGGCGC  
LeuSerTyrIleGlnIleIleGlnAlaIleLeuArgIleHisThrAlaAspGlyArgArg

Figure 13

721 CGGGCTTTTCAACTTGTGGAGCCCATGTAACCGTGGTCACCGTGACTATGTGCCCTGT  
ArgAlaPheSerThrCysGlyAlaHisValThrValValThrValTyrTyrValProCys  
TM-VI  
781 GCCTTCATCTACCTGAGGCCTGAAACCAACAGCCCCCTGGATGGGGCAGCTGCCCTAGTC  
AlaPheIleTyrLeuArgProGluThrAsnSerProLeuAspGlyAlaAlaAlaLeuVal  
841 CCCACGGCCATCACTCCTTTCCTCAACCCCTTATCTACACTCTGCGGAACCAAGAGGTG  
ProThrAlaIleThrProPheLeuAsnProLeuIleTyrThrLeuArgAsnGlnGluVal  
TM-VII  
901 AAGCTGGCCCTGAAAAGAATGCTCAGAAGCCCAAGAACTCCGAGTGAGGTTTGAAAGTGT  
LysLeuAlaLeuLysArgMetLeuArgSerProArgThrProSerGluVal\*\*\*  
961 CTTTCTCCCACTAGGGAAGCTGCCACAATTAGAATTTATTATAATGTTTAGGCTTCGGTA  
1021 ACTTTTTTCTTTTCTTCTGTTTTTCTCTTTTATATAGCCATACTGTATGATCAAACAC  
1081 AGTTTAAGGTAAAATACTAACTTTCTAACAGTTCCTTAGTATCCTCTCAAGATAACTCTC  
1141 AGCCACTGCAAGAGTAGAGAATGAGACCAAATTCACAAACTAAACCACATTAAACAAT  
1201 CCAGAAGAAAGAATGCAATAGTGTATTTCCAATGTCTCAGTAATAAA

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Figure 14

1 GGCAACCTAAAAGCAAGCATGGACAGTTCCTTGGTGAATAACCAAAAACAAGATGGAGTC  
61 TCGCTCTGTTGCCAGGCTGGAGTGTAGTGGCGCCATCTCGGCTCGCTGCGGTCTCCGCC  
121 TCCCGGGTTCAGGCGATTCTCCGGCCTCAGCCTCCCGGGTGGTGGGATTGCAGGAATA  
181 GAACTAAAGCGAGGTTAATTTCCACAGTGAGAACATGCTCCAGACATCCGAGCACCAGTG  
241 TGGCTCTGGAACTCCACAGATACCACAGGACTAGAAAATAACTGGACAATGGGATGTTCT  
301 TATCTTGCCCGAACTGAGGGATATAAAAAGCTCCAAAGACAAAGAAAGTACCATCCACCC  
361 ATCCCAAAAGAAATTATCCTTCCTTCTGAAAATAAGACTGCAAAAAGACATGGGAAAGAC  
MetGlyLysThr  
421 CAAAAACACATCGCTGGATGCCGTGGTGACAGATTTCAATCTTCTGGGTTTGTCTCACCC  
LysAsnThrSerLeuAspAlaValValThrAspPheIleLeuLeuGlyLeuSerHisPro  
481 CCCAAATCTAAGAAGCCTCCTCTCTGGTCTTCTTCATCATTTACATCCTCACTCAGCT  
ProAsnLeuArgSerLeuLeuPheLeuValPhePheIleIleTyrIleLeuThrGlnLeu  
TM-I  
541 GGGGAACCTGCTCATTCTGCTCACCATGTGGGCTGACCCGAAGCTCTGTGCTCGCCCCAT  
GlyAsnLeuLeuIleLeuLeuThrMetTrpAlaAspProLysLeuCysAlaArgProMet  
601 GTACATTCTTCTGGGAGTGCTCTCATTCTGGACATGTGGCTCTCCTCAGTCACCGTTCC  
TyrIleLeuLeuGlyValLeuSerPheLeuAspMetTrpLeuSerSerValThrValPro  
TM-II  
661 TCGGCTTATTTTGGATTTTACTCCTTCCATCAAGGCTATCCCGTTTGGTGGCTGTGTGGC  
ArgLeuIleLeuAspPheThrProSerIleLysAlaIleProPheGlyGlyCysValAla  
721 TCAACTGTATTTCTTTCACTTCCTGGGCAGCACCCAGTGCTTCCTCTACACCTTGATGGC  
GlnLeuTyrPhePheHisPheLeuGlySerThrGlnCysPheLeuTyrThrLeuMetAla  
TM-III  
781 CTATGACAGGTACCTAGCAATATGTCAGCCCTGCACTACCCAGTGCTCATGAATGGGAG  
TyrAspArgTyrLeuAlaIleCysGlnProLeuHisTyrProValLeuMetAsnGlyArg  
841 GTTATGCACAGTCCTTGTGGCTGGAGCTTGGGTCGCCGGCTCCATGCATGGGTCTATCCA  
LeuCysThrValLeuValAlaGlyAlaTrpValAlaGlySerMetHisGlySerIleGln  
TM-IV  
901 GGCCACCTTGACCTTCCGCTGCCCTACTGTGGGCCCAATCAGGTGGATTACTTTATCTG  
AlaThrLeuThrPheArgLeuProTyrCysGlyProAsnGlnValAspTyrPheIleCys

Figure 15

961 TGACATCCGCGCAGTATTGAGACTGGCCTGTGCTGACACAACGTCAATGAGCTTGTGAC  
AspIleArgAlaValLeuArgLeuAlaCysAlaAspThrThrValAsnGluLeuValThr

1021 CTTTGTGGACGTCAGGGTAGTGGCCGCCAGTTGCTTCATGTTAATTCTGCTCTCCTATGC  
PheValAspValArgValValAlaAlaSerCysPheMetLeuIleLeuLeuSerTyrAla

TM-V

1081 CAACATAGTCCATGCCATCCTGAAGATACGCACCGCTGATGGGAGGCGCCGGGCCTTCTC  
AsnIleValHisAlaIleLeuLysIleArgThrAlaAspGlyArgArgArgAlaPheSer

1141 CACCTGTGGCTCCACCTAATCGTGGTCACAGTCTACTATGTCCCCTGTATTTTCATCTA  
ThrCysGlySerHisLeuIleValValThrValTyrTyrValProCysIlePheIleTyr

TM-VI

1201 CCTTAGGGCTGGCTCCAAAGACCCCTGGATGGGGCAGCGGCTGTGTTTACACTGTTGT  
LeuArgAlaGlySerLysAspProLeuAspGlyAlaAlaAlaValPheTyrThrValVal

1261 CACTCCATTACTGAACCCCTCATCTATACTGAGGAACCAGGAAGTGAAGTCTGCCCT  
ThrProLeuLeuAsnProLeuIleTyrThrLeuArgAsnGlnGluValLysSerAlaLeu

TM-VII

1321 GAAGAGGATAACAGCAGGTTGAAGGACTGAATGAAAATAAGTAACTACATCTGCATCATT  
LysArgIleThrAlaGly\*\*\*

1381 ATCACTGCCACTCTCTTCAGCTACTGCTGCATGTGACAAATGCCCAATAAA



Figure 16

1    CAGCAGCTTGTCTTCGTCGATTTCTGCTATTCTCTGTCATTACTCCCA  
51    AAATGCTGGTGAACCTTCCTAGGAAAGAAGAATACAATCCTTTACTCTGAG  
101    TGCATGGTCCAGCTCTTTTCTTTGTGGTCTTTGTGGTGGCTGAGGGTTA  
151    CCTCCTGACTGCCATGGCATATGATCGCTATGTTGCCATCTGTAGCCAC  
201    TGCTTTATAATGCGATCATGTCCTCATGGGTCTGCTCACTGCTAGTGCTG  
251    GCTGCCTTCTTCTTGGGCTTCTCTCTGCCTTGACTCATACAAGTGCCAT  
301    GATGAAACTGTCCTTTTGCAAATCCACATTATCAACCATTACTTCTGTG  
351    ATGTTCTTCCCCTCCTCAATCTCTCCTGCTCCAACACACACCTCAATGAG  
401    CTTCTACTTTTATCATTGCGGGTTTAACACCTTGGTGCCCACCCTAGC

Figure 17

1    CATGGTAGGCAACCTTGGCTTGATCACTCTTTTCGGTCTAAATTCTCACC  
51    TCCACACACCAATGTACTATTTCTCTTCAATCTCTCCTTCATTGATCTC  
101   TGTTACTCCTCTGTTTTCACTCCCAAAATGCTAATGAACTTTGTGTCAAA  
151   AAAGAATATTATCTCCAATGTTGGGTGCATGACTCGGCTGTTTTTCTTTC  
201   TCTTTTTCGTCATCTCTGAATGTTACATGTTGACCTCAATGGCATATGAT  
251   CGCTATGTGGCCATCTGTAATCCATTGCTGTATAAGGTCACCATGTCCCA  
301   TCAGGTCTGTTCTATGCTCACTTTTGCTGCTTACATAATGGGATTGGCTG  
351   GAGCCACGGCCACACCGGGTGCATGTTTACTACCTTCTGCAGTGCT  
401   AATATCATTAACCATTACTTGTGTGACATACTCCCCCTCCTCCAGCTTTC  
451   CTGCACCAGCACCTATGTCAACGAGGTGGTTGTTCTCATTTGTGTTGGTA  
501   CTAATATCACGGTACCCAGTTGTACCATCCTCATTTCTTATGTTTTCATT  
551   GTCACTAGCATTCTTCATATCAAATCCACTCAAGGAAGATCAAAAGCCTT  
601   CAGTACTTGTAGCTCTCATGTCATTGCTCTGTCTCTG

Figure 18

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1    CATGGTAGGCAACCTTGGCTTGATCATTCTTTTCGGTCTAAATTCTCACC  
51    TCCACACACCAATGTACTATTTCTCTTCAATCTCTCCTTCATTGATCTC  
101   TGTTACTCCTCTGTTTTCACCTCCCAAAATGCTAATGAACCTTGTATCAAA  
151   AAAGAATATTATCTCCTATGTTGGGTGCATGACTCAGCTGTTTTCTTTTC  
201   TCTTTTGTGTCATCTCTGAATGCTACATATTGACCTCAATGGCATATGAT  
251   CGCTATGTGGCCATCTGTAATCCATTGCTGTATAAGGTCACCATGTCCCA  
301   TCAGGTCGTCTTCTATGCTCACTTTTGCTGCTTACATAATGGGATTGGCTG  
351   GAGCCACGGCCCACACCGGGTGCATGCTTAGACTCACCTTCTGCAGTGCT  
401   AATATCATCAACCATTAATTGTGTGACATACTCCCCCTCCTCCAGCTTTTC  
451   CTGCACCAGCACCTATGTCAACGAGGTGGTTGTTCTCATTGTTGTGGGTA  
501   TTAATATCATGGTACCCAGTTGTACCATCCTCATTTCCTTATGTTTTTCATT  
551   GTCAC TAGCATTCTTCATATCAAATCCACTCAAGGAAGATCAAAAGCCTT  
601   CAGTACTTGTAGCTCTCATGTCATGCTCTGTCTCTG

Figure 19

1    CCTTTATAGATCTCTGTTATTCCTGTTGTTTACCCCCAAAATGCTGAAT  
51    GACTTTGTTTCAGAAAGTATCATCTCTTATGTGGGATGTATGACTCAGCT  
101   ATTTTCTTCTGTTTCTTTGTCAATTCTGAGTGCTATGTGTTGGTATCAA  
151   TGGCCTATGATCGCTATGTGGCCATCTGCAACCCCTGCTCTACATGGTC  
201   ACCATGTCCCCAAGGGTCTGCTTCTGCTGATGTTTGGTTCCTATGTGGT  
251   AGGGTTTGCTGGGGCCATGGCCCACACTGGAAGCATGCTGCGACTGACCT  
301   TCTGTGATTCCAACGTCATTGACCATTATCTGTGTGACGTTCTCCCCCTC  
351   TTGCAGCTCTCCTGCACCAGCACCATGTCAGTGAGCTGGTATTTTTCAT  
401   TGTGTTGGAGTAATCACCATGCTATCCAGCATAAGCATCGTCATCTCTT  
451   ACGCTTTGATACTCTCCAACATCCTCTGTATTCCTTCTGCAGAGGGCAGA  
501   TCCAAAGCC

Figure 20

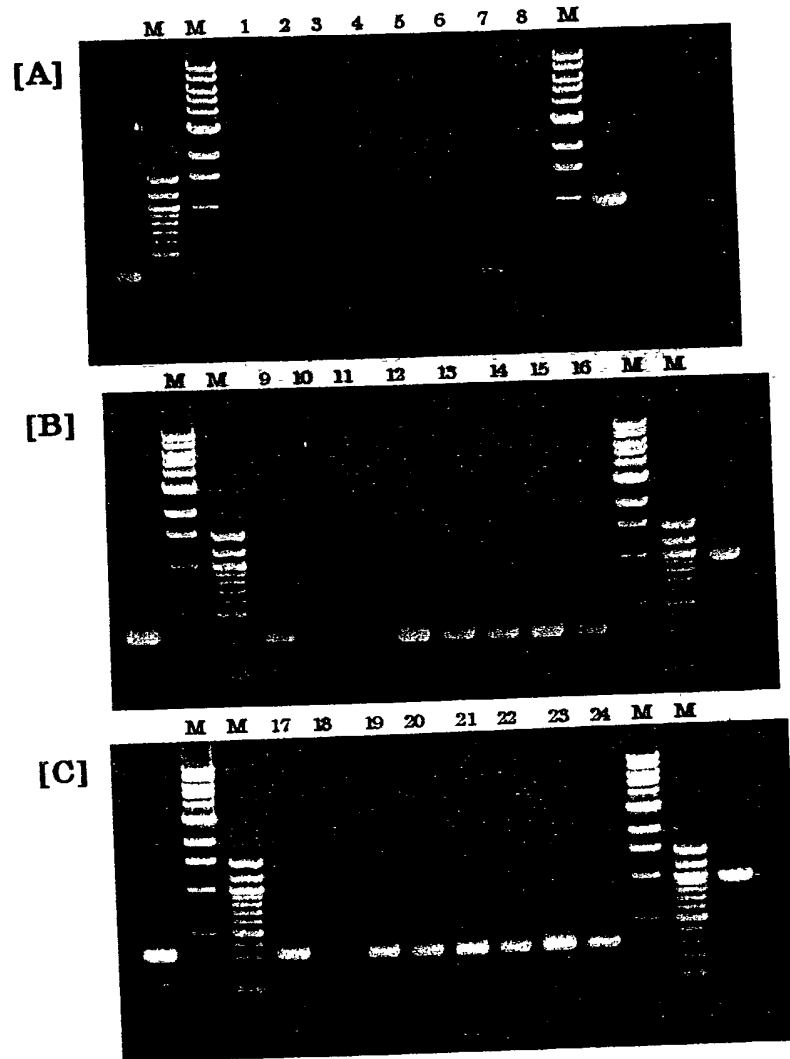


Figure 21

09/807132

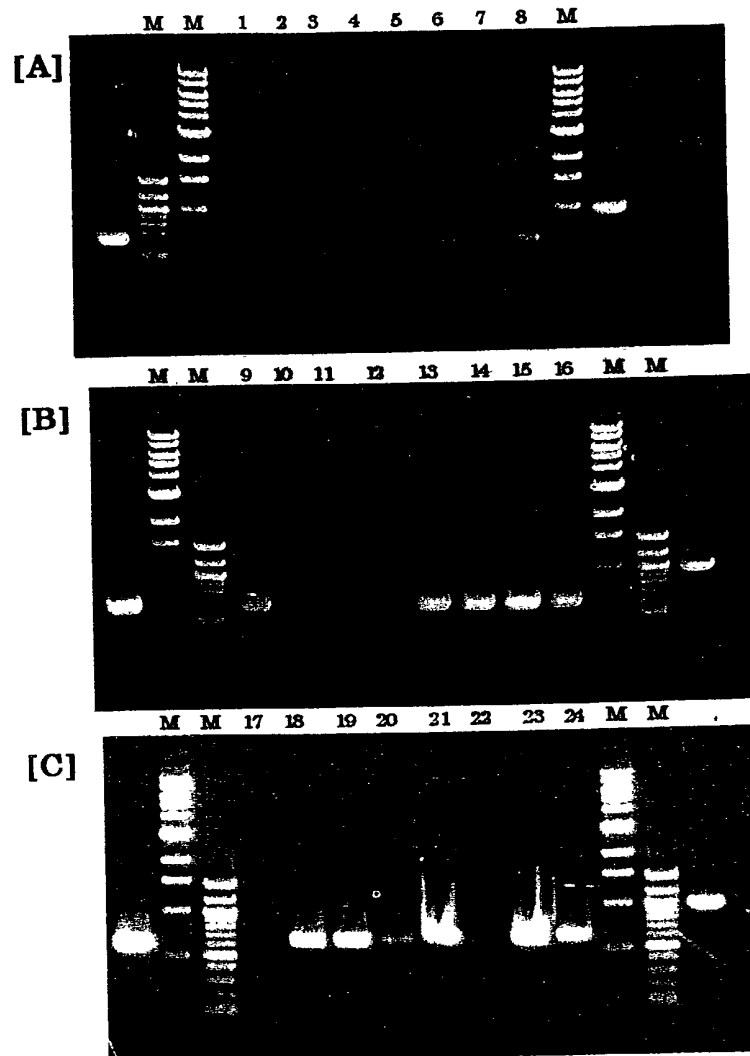


Figure 22

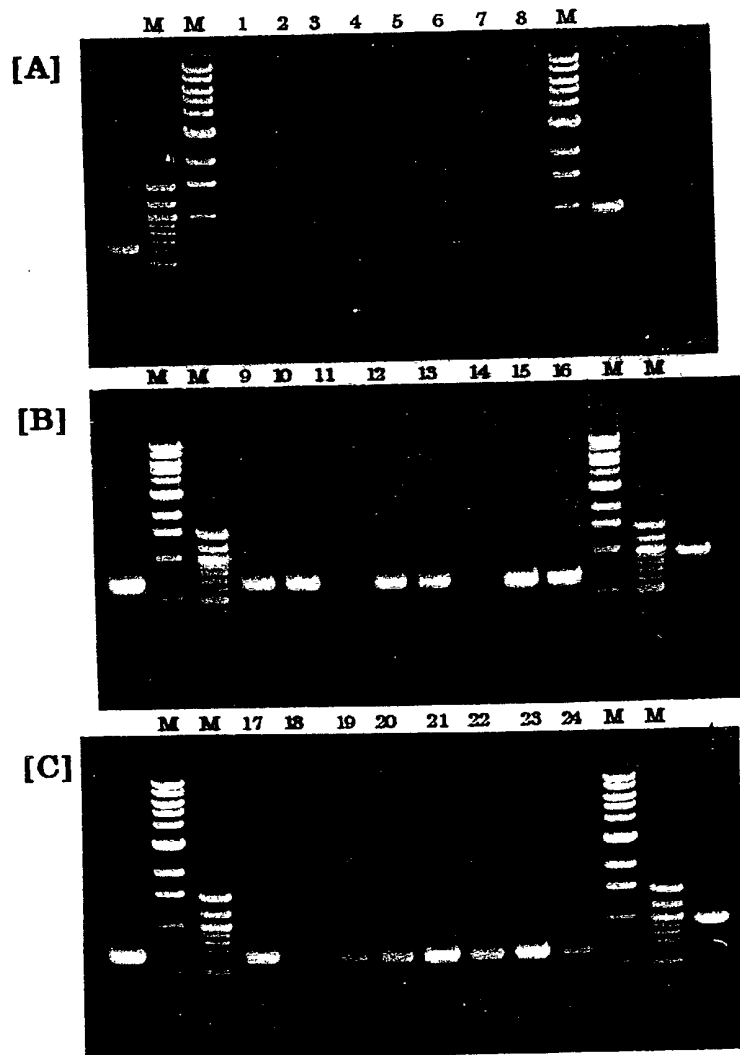


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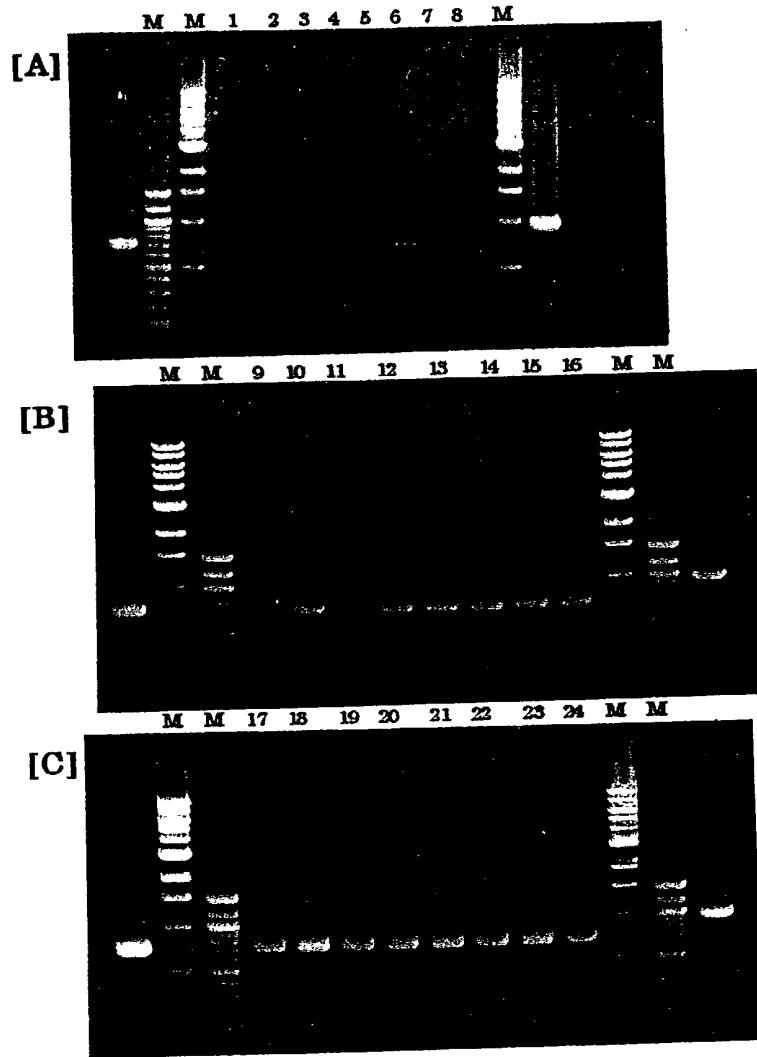




Figure 24

1 AAATGCCTAAAGAAGAATGACCATGGAAAAATTATTCTATGGCAGCTCAGTTTGTCTTAGA  
MetThrMetGluAsnTyrSerMetAlaAlaGlnPheValLeuAsp

61 TGGTTTAACACAGCAAGCAGAGCTCCAGCTGCCCCCTTCTCCTGTTCTCTGGGAATCTA  
GlyLeuThrGlnGlnAlaGluLeuGlnLeuProLeuPheLeuLeuPheLeuGlyIleTyr

121 TGTGGTCACAGTAGTGGGCAACCTGGGCATGATTCTCCTGATTGCAGTCAGCCCTCTACT  
ValValThrValValGlyAsnLeuGlyMetIleLeuLeuIleAlaValSerProLeuLeu  
TM-I

181 TCACACCCCATGTACTATTCTCCTCAGCAGCTTGTCCTTCGTCGATTCTGCTATTCTCTC  
HisThrProMetTyrTyrPheLeuSerSerLeuSerPheValAspPheCysTyrSerSer  
TM-II

241 TGTCACTACTCCCAAAATGCTGGTGAACCTCCTAGGAAAGAAGAATACAATCCTTTACTC  
ValIleThrProLysMetLeuValAsnPheLeuGlyLysLysAsnThrIleLeuTyrSer

301 TGAGTGCATGGTCCAGCTCTTTTCTTTTGGTCTTTTGGTGGCTGAGGGTTACCTCCT  
GluCysMetValGlnLeuPhePhePheValValPheValValAlaGluGlyTyrLeuLeu  
TM-III

361 GACTGCCATGGCATATGATCGCTATGTTGCCATCTGTAGCCCACTGCTTTATAATGCGAT  
ThrAlaMetAlaTyrAspArgTyrValAlaIleCysSerProLeuLeuTyrAsnAlaIle

421 CATGTCCTCATGGGTCTGCTCACTGCTAGTGTGGTGCCTTCTTCTTGGGCTTTCTCTC  
MetSerSerTrpValCysSerLeuLeuValLeuAlaAlaPhePheLeuGlyPheLeuSer  
TM-IV

481 TGCCTTGACTCATACAAGTGCCATGATGAACTGTCTTTTGCAAATCCACATTATCAA  
AlaLeuThrHisThrSerAlaMetMetLysLeuSerPheCysLysSerHisIleIleAsn

541 CCATTACTTCTGTGATGTTCTTCCCTCCTCAATCTCTCCTGCTCCAACACACACCTCAA  
HisTyrPheCysAspValLeuProLeuLeuAsnLeuSerCysSerAsnThrHisLeuAsn

601 TGAGCTTCTACTTTTATCATTGCGGGGTTTAACACCTTGGTGGCCACCTAGCTGTTGC  
GluLeuLeuLeuPheIleIleAlaGlyPheAsnThrLeuValProThrLeuAlaValAla  
TM-V

661 TGTCTCCTATGCCTTCATCTCTACAGCATCCTTCACATCCGCTCCTCAGAGGGCCGGTC  
ValSerTyrAlaPheIleLeuTyrSerIleLeuHisIleArgSerSerGluGlyArgSer

721 CAAAGCTTTTGAACATGCAGCTCTCATCTCATGGCTGTGGTGATCTTCTTTGGGTCCAT  
LysAlaPheGlyThrCysSerSerHisLeuMetAlaValValIlePhePheGlySerIle  
TM-VI

781 TACCTTCATGTATTTCAGCCCCCTTCAAGTAACTCCCTGGACCAGGAGAAGGTGTCTCTC  
ThrPheMetTyrPheLysProProSerSerAsnSerLeuAspGlnGluLysValSerSer

841 TGTGTTCTACACCACGGTGATCCCCATGCTGAACCTTTAATATACAGTCTGTAATCACA  
ValPheTyrThrThrValIleProMetLeuAsnProLeuIleTyrSerLeu\*\*\*  
TM-VII

901 GCACTTTGGAAGGCTGAGGCAGGTTGCTTGAGTCCAGTTTGAGACCATCCTGGGGAACA

961 TAGTGCGATCTTGTCTTCTTCCACTGCCTAAAACTTCAATGCTCAATTTTACTTGCAAT

1021 TTCCTCTCCTGACATGGAGAATGTTGGCTTGAATGTTC

Figure 25

1 ATTTTGAAGACAAAAATGCTGGCTAGAAACAACCTCTTAGTGACTGAATTTATTCTTG  
MetLeuAlaArgAsnAsnSerLeuValThrGluPheIleLeuAla

61 CTGGATTAAACAGATCGTCCAGAGTTCTGGCAACCCTTCTTTTCTGTTCCCTAGTGATCT  
GlyLeuThrAspArgProGluPheTrpGlnProPhePhePheLeuPheLeuValIleTyr

121 ACATTGTCACCATGGTAGGCAACCTTGGCTTGATCACTCTTTTCGGTCTAAATTCTCACC  
IleValThrMetValGlyAsnLeuGlyLeuIleThrLeuPheGlyLeuAsnSerHisLeu  
TM-I

181 TCCACACACCAATGTACTATTTCTCTTCAATCTCTCTTCATTGATCTCTGTTACTCCT  
HisThrProMetTyrTyrPheLeuPheAsnLeuSerPheIleAspLeuCysTyrSerSer  
TM-II

241 CTGTTTTCACTCCCAAAATGCTAATGAACTTTGTGTCAAAAAGAATATTATCTCCAATG  
ValPheThrProLysMetLeuMetAsnPheValSerLysLysAsnIleIleSerAsnVal

301 TTGGGTGCATGACTCGGCTGTTTTCTTCTCTTTTTCGTCATCTCTGAATGTTACATGT  
GlyCysMetThrArgLeuPhePhePheLeuPhePheValIleSerGluCysTyrMetLeu  
TM-III

361 TGACCTCAATGGCATATGATCGCTATGTGGCCATCTGTAATCCATTGCTGTATAAGGTCA  
ThrSerMetAlaTyrAspArgTyrValAlaIleCysAsnProLeuLeuTyrLysValThr

421 CCATGTCCCATCAGGTCTGTTCTATGCTCAGTTTGTGCTTACATAATGGGATTGGCTG  
MetSerHisGlnValCysSerMetLeuThrPheAlaAlaTyrIleMetGlyLeuAlaGly  
TM-IV

481 GAGCCACGGCCACACCGGGTGCATGTTTAGACTCACCTTCTGCAGTGCTAATATCATTA  
AlaThrAlaHisThrGlyCysMetPheArgLeuThrPheCysSerAlaAsnIleIleAsn

541 ACCATTACTTGTGTGACATACTCCCCCTCCTCCAGCTTTCCTGCACCAGCACCTATGTCA  
HisTyrLeuCysAspIleLeuProLeuLeuGlnLeuSerCysThrSerThrTyrValAsn

601 ACGAGGTGGTTGTTCTCATTGTTGTGGTACTAATATCACGGTACCCAGTTGTACCATCC  
GluValValValLeuIleValValGlyThrAsnIleThrValProSerCysThrIleLeu  
TM-V

661 TCATTCTTATGTTTTCATTGTCAGTCTCTCATATCAAATCCACTCAAGGAAGAT  
IleSerTyrValPheIleValThrSerIleLeuHisIleLysSerThrGlnGlyArgSer

721 CAAAAGCCTTCAGTACTTGTAGCTCTCATGTGCTGCTCTGTTTTCGGTTCAG  
LysAlaPheSerThrCysSerSerHisValIleAlaLeuSerLeuPhePheGlySerAla  
TM-VI

781 CGGCATTTCATGTATATTAAATATTCTTCTGGATCTATGGAGCAGGGAAGTTTTCCTG  
AlaPheMetTyrIleLysTyrSerSerGlySerMetGluGlnGlyLysValPheSerVal

841 TTTTCTACACTAATGTGGTGGCCATGCTCAATCCCCTCATCTACAGTTGAGGAACAAGG  
PheTyrThrAsnValValProMetLeuAsnProLeuIleTyrSerLeuArgAsnLysAsp  
TM-VII

901 ATGTCAAAGTTGCACTGAGGAAAGCTCTGATTAAATTCAGAGGAGAAATATATTCTAAT  
ValLysValAlaLeuArgLysAlaLeuIleLysIleGlnArgArgAsnIlePhe\*\*\*

961 TAGAAGCAGTAATGATGTAAAAAATGAAGGACTTCAAATTTTTATTAGTGTTTTCAT

1021 GAAGAGATTTTGTGTTTCTACAGATGGTGTATGTGTGATTTAATAAA

Figure 26

1 ATTTTGAAGACAAAAATGCTGGCTAGAAACAACCTTAGTGACTGAATTATTCTTG  
MetLeuAlaArgAsnAsnSerLeuValThrGluPheIleLeuAla

61 CTGGATTAACAGATCGTCCAGAGTTCGGCAACCCCTCTTTTCTGTTTCTAGTGATCT  
GlyLeuThrAspArgProGluPheArgGlnProLeuPhePheLeuPheLeuValIleTyr

121 ACATTGTCACCATGGTAGGCAACCTTGGCTTGATCATTCTTTTCGGTCTAAATCTCACC  
IleValThrMetValGlyAsnLeuGlyLeuIleIleLeuPheGlyLeuAsnSerHisLeu  
TM-I

181 TCCACACACCAATGTACTATTTCCTCTTCAATCTCTCCTTCATTGATCTCTGTTACTCCT  
HisThrProMetTyrTyrPheLeuPheAsnLeuSerPheIleAspLeuCysTyrSerSer  
TM-II

241 CTGTTTTCACTCCCAAATGCTAATGAACCTTGTATCAAAAAAGAATATTATCTCCTATG  
ValPheThrProLysMetLeuMetAsnPheValSerLysLysAsnIleIleSerTyrVal

301 TTGGGTGCATGACTCAGCTGTTTTCTTTCTCTTTTGTGCATCTCTGAATGCTACATAT  
GlyCysMetThrGlnLeuPhePhePheLeuPhePheValIleSerGluCysTyrIleLeu  
TM-III

361 TGACCTCAATGGCATATGATCGCTATGTGGCCATCTGTAATCCATTGCTGTATAAGGTCA  
ThrSerMetAlaTyrAspArgTyrValAlaIleCysAsnProLeuLeuTyrLysValThr

421 CCATGTCCCATCAGGTCTGTTCTATGCTCAGTTTGTCTGCTTACATAATGGGATTGGCTG  
MetSerHisGlnValCysSerMetLeuThrPheAlaAlaTyrIleMetGlyLeuAlaGly  
TM-IV

481 GAGCCACGGCCACACCGGGTGCATGCTTAGACTCACCTTCTGCAGTGCTAATATCATCA  
AlaThrAlaHisThrGlyCysMetLeuArgLeuThrPheCysSerAlaAsnIleIleAsn

541 ACCATTACTTGTGTGACATACTCCCCCTCCTCCAGCTTTCCTGCACCAGCACCTATGTCA  
HisTyrLeuCysAspIleLeuProLeuLeuGlnLeuSerCysThrSerThrTyrValAsn

601 ACGAGGTGGTTGTTCTCATTGTTGTGGGTATTAATATCATGGTACCCAGTTGTACCATCC  
GluValValValLeuIleValValGlyIleAsnIleMetValProSerCysThrIleLeu  
TM-V

661 TCATTTCTTATGTTTTCTTGTGCTAGCATTCTTCATATCAAATCCACTCAAGGAAGAT  
IleSerTyrValPheIleValThrSerIleLeuHisIleLysSerThrGlnGlyArgSer

721 CAAAAGCCTTCAGTACTGTAGCTCTCATGTCATTGCTCTGTCTCTGTTTTTGGGTCAG  
LysAlaPheSerThrCysSerSerHisValIleAlaLeuSerLeuPhePheGlySerAla  
TM-VI

781 CGGCATTCATGTATATTAAATATTCTTCTGGATCTATGGAGCAGGAAAAGTTTCTCTG  
AlaPheMetTyrIleLysTyrSerSerGlySerMetGluGlnGlyLysValSerSerVal

841 TTTTCTACACTAATGTGGTGCCCATGCTCAATCCTCTCATCTACAGTTTGAGGAACAAGG  
PheTyrThrAsnValValProMetLeuAsnProLeuIleTyrSerLeuArgAsnLysAsp  
TM-VII

901 ATGTCAAAGTTGCACTGAGGAAAGCTCTGATTAAAATTCAGAGAAGAAATATATTCTAAT  
ValLysValAlaLeuArgLysAlaLeuIleLysIleGlnArgArgAsnIlePhe\*\*\*

961 TAGAAGCAGTAATAATGTAAAACGATTGAAGAACTTTAAATTTTTATTAGTGTGTTCCAT

1021 GAAGAGATTTTGTGTTTCTACAGATGGTGTATGTGTGATTTAATAAA

Figure 27

1 ACAGCTCGCCAAGAGAGAATGACTCTGAGAAACAGCTCCTCAGTGACTGAGTTTATCCTT  
MetThrLeuArgAsnSerSerSerValThrGluPheIleLeu

61 GTGGGATTATCAGAACAGCCAGAGCTCCAGCTCCCTCTTTTCCTTCTATTCTTAGGGATC  
ValGlyLeuSerGluGlnProGluLeuGlnLeuProLeuPheLeuLeuPheLeuGlyIle

121 TATGTGTTCACTGTGGTGGGCAACTGGGCTTGATCACCTTAATTGGGATAAATCCTAGC  
TyrValPheThrValValGlyAsnLeuGlyLeuIleThrLeuIleGlyIleAsnProSer  
TM-I

181 CTTACACCCCCATGTACTTTTTCCTCTTCAACTTGTCCTTTATAGATCTCTGTTATTCC  
LeuHisThrProMetTyrPhePheLeuPheAsnLeuSerPheIleAspLeuCysTyrSer  
TM-II

241 TGTGTGTTTACCCCCAAATGCTGAATGACTTTGTTTCAGAAAGTATCATCTCTTATGTG  
CysValPheThrProLysMetLeuAsnAspPheValSerGluSerIleIleSerTyrVal

301 GGATGTATGACTCAGCTATTTTCTTCTGTTTCTTTGTCAATTCTGAGTGCTATGTGTG  
GlyCysMetThrGlnLeuPhePhePheCysPhePheValAsnSerGluCysTyrValLeu  
TM-III

361 GTATCAATGGCCTATGATCGCTATGTGGCCATCTGCAACCCCTGCTCTACATGGTCACC  
ValSerMetAlaTyrAspArgTyrValAlaIleCysAsnProLeuLeuTyrMetValThr

421 ATGTCCCCAAGGTCTGCTTTCTGCTGATGTTTGGTTCCTATGTGGTAGGGTTTGCTGGG  
MetSerProArgValCysPheLeuLeuMetPheGlySerTyrValValGlyPheAlaGly  
TM-IV

481 GCCATGGCCACACTGGAAGCATGCTGCGACTGACCTTCTGTGATTCCAACGTCATTGAC  
AlaMetAlaHisThrGlySerMetLeuArgLeuThrPheCysAspSerAsnValIleAsp

541 CATTATCTGTGTGACGTTCTCCCCCTCTTGACGCTCTCCTGCACCAGCACCATGTCAGT  
HisTyrLeuCysAspValLeuProLeuLeuGlnLeuSerCysThrSerThrHisValSer

601 GAGCTGGTATTTTTCATTGTTGTTGGAGTAATCACCATGCTATCCAGCATAAGCATCGTC  
GluLeuValPhePheIleValValGlyValIleThrMetLeuSerSerIleSerIleVal  
TM-V

661 ATCTCTTACGCTTTGATACTCTCCAACATCCTCTGTATTCCTTCTGCAGAGGGCAGATCC  
IleSerTyrAlaLeuIleLeuSerAsnIleLeuCysIleProSerAlaGluGlyArgSer

721 AAAGCCTTTAGCACATGGGGCTCCACATAATTGCTGTTGCTCTGTTTTTTGGGTACAGG  
LysAlaPheSerThrTrpGlySerHisIleIleAlaValAlaLeuPhePheGlySerGly  
TM-VI

781 ACATTACCTACTTAACAACATCTTTTCCTGGCTCTATGAACCATGGCAGATTTCCTCA  
ThrPheThrTyrLeuThrThrSerPheProGlySerMetAsnHisGlyArgPheAlaSer

841 GTCTTTTACACCAATGTGGTCCCATGCTTAACCCCTTCGATCTACAGTTTGAGGAATAAG  
ValPheTyrThrAsnValValProMetLeuAsnProSerIleTyrSerLeuArgAsnLys  
TM-VII

901 GATGATAAACTTGCCCTGGGCAAAACCTGAAGAGAGTGCTCTTCTAATGGGTCTCTTCA  
AspAspLysLeuAlaLeuGlyLysThrLeuLysArgValLeuPhe\*\*\*

961 TATCACTGGCAACCGA

Figure 28

```

OLF1 MEFTD-RMYT -LVTEFILLG FPTRPELQIV LFLMFLTYA IILIGNIGLM LI RIDPHLO
OLF2 M---D--NQS S-TPGFLLLG FSEHPGLGRT LFVDVITSYL LTLVGNTLII LI ALDTKLE
OLF3 MG-TD--NQT -WVSEFILLG LSSDWDTRVS LFVLFVLMYV VTVLGNCLIV LI RLD SRLH
11-1 M--TME-NYS M-AAQFVLDG LTQQAELQLP LFLFLGIYV VTVVGNLGM I LI AVSPLLE
      *      *      * * *      **      *      **      **      *

OLF1 TPMYFFLSNL SPVDLCYFSD IVPKMLVNFL SENKSISYYG CALQFYFFCT FADTESFILA
OLF2 SPMYFFLSNL SFIDLCPPTS CVPOMLANLW GPKKTISFLD CSVOIFIFLS LGTTECILMK
OLF3 TPMYFFLTNL SLVDVSYATS VVPQLLAHFL AEHKAIPFQS CAAQLFFSLA LGGIEFVLLA
11-1 TPMYFFLSSL SPVDFCYSSV ITPKMLVNFL GKKNITILYSE CMVOLFFFV FVVAEGYLLT
      *** * * * *      * *      *      * *      *

OLF1 AMAYDRYVAI CNPLLYTVVM SRGICMRLIV LSYLGGNMSS LVHTSFAPIL KYCDKNVINH
OLF2 VMAFDRYVAV COPLHYATII HPRLCWQLAS VAWVIGLVGS VVQTPSTLHL PFCPDROVDD
OLF3 VMAYDRYVAV CDALRYSAIM HGGLCARLAI TSWVSGFISS PVQTAITFOL PMCRNKFDH
11-1 AMAYDRYVAI CSPLLYNAM SSWVCSLLVL AAFFLGFLSA LHTSAMMKL SFCKSHIINH
      ** * * * *      * *      *      *      *      *

OLF1 FFCDLPLLLK LSCDTTINE WLLSTYGSSV EIICFIIIII SYFFILLSVL KIRSFSGRKK
OLF2 FVCEVPALIR LSCEDTSYNE IQVAVASVFI LUVPLSLILV SYGAITWAVL RINSATAWRK
OLF3 ISCELLAVVR LACVDTSNE VTMVSSIVL LMTPLCLVLL SYIQIISTIL KIQSREGRKK
11-1 YFCDLVPLLN LSCSNTHLNE LLLFIIAGFN TLVPTLAVAV SYAFILYSIL HIRSSEGRSK
      *      * * * *      ** *      * * *      *

OLF1 TFSTCASHLT SVTIYOGTLL FIYSRPSYLY SPNTDKIISV FYTIFIPVLN PLIYSLRNKD
OLF2 AFGTCSSHLT VVTLFYSSVI AVYLOPKNPY AQGRGKFFGL FYAVGTPSLN PLVYTLRNKE
OLF3 APHTCASHLT VVALCYGVAI FTYIQPHSSP SVLQEKLFV FYAILTPMLN PMIYSLRNKE
11-1 AFGTCSSHLM AVVIFGFSIT FMYFKPPSSN SLDQEKVSSV FYTTVIPMLN PLIYSL-----
      * * * *      *      * *      *      * *      * * * *

OLF1 VKDAAEKVLR SKVDS--S
OLF2 IKRALRRLLG KERDSRESWR AA
OLF3 VKGAWQKLLW KFSG-LTSKL AT
11-1 -----

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Figure 29

```

OLF2  M--DNQ SSTPGFLLG FSEHPGLGRT LFVDVITSYL LTLVGNTLII LLSALDTKLH
OLF3  MGT-DNQ TWVSEFILLG LSSDWTRVS LFVLFLVMYV VTVLGNCLIV LLIRLDSRLH
11-2  MLAR-NN SLVTEFILAG LTRPEFWQP FFFLFLVIYI VTMVGNLGLI TLFGNLSHLH
      *  *      * * *      *      * * * *      *      **
OLF2  SPMYFFLSNL SFLDLCFTTS CVPQMLANLW GPKKTISFLD CSVQIFIFLS LGTTECILMK
OLF3  TPMYFFLTNL SLVDVSYATS VVPQLLAHFL AEHKAIPPQS CAAQLFFSLA LGGIEFVLLA
11-2  TPMYFFLFNL SFIDLCYSSV FTPKMLMNFV SKKNIISNVG CMTRLFFFLF FVISECYMLT
      *** ** * *      * *      *      * * *      *
OLF2  VMAFDRYVAV CQPLHYATII HPRLCWQLAS VAWVIGLVGS VVQTPSTLHL PFCPDRQVDD
OLF3  VMAYDRYVAV CDALRYSAIM HGGLCARLAI TSWVSGFISS PVQTAITFQL PMCRNKFIDH
11-2  SMAYDRYVAI CNPLLYKVTM SHQVCSMLTF AAYIMGLAGA TAHTGCMFRL TFCSANIINH
      ** ***** * * *      * *      *      * *
OLF2  FVCEVPALIR LSCEDTSYNE IQVAVASVFI LVVPLSLILV SYGAIWAVL RINSATAWRK
OLF3  ISCELLAVVR LACVDTSSNE VTIMVSSIVL LMTPLCLVLL SYIQIISTIL KIQSREGRKK
11-2  YLCDILPLLQ LSCTSTYVNE VVVLIVVGTN ITVPSTILI SYVFIVTSIL HIKSTQGRSK
      *      * * * *      *      * * * *      *      *
OLF2  AFGTCSSHLT VTLFYSSVI AVYLQKPNPY AQGRGKFFGL FYAVGTPSLN PLVYTLRNKE
OLF3  AFHTCASHLT VVALCYGVAI FTYIQPHSSP SVLQEKLFVS FYAILTPMLN PMIYSLRNKE
11-2  AFSTCSSHVI ALSLFFGSAA FMYIKY-SSG SMEQGVFSV FYTNVVPMLN PLIYSLRNKD
      ** ** *      *      *      * *      * * * *      *
OLF2  IKRALRRLLG KERDSRESWR AA
OLF3  VKGAWQKLLW KFSGL-TSKL AT
11-2  VKVALRKALI KIQ-RRN--I -F
      * *      * *

```

OLF2	M--- <u>DNQ</u>	SSTPGFLLLG	FSEHPGLGRT	LFVDVITSYL	LTLVGNLII	LLSALDTKHL	
OLF3	MGT- <u>DNQ</u>	TWVSEFILLG	LSSDWDTRVS	LFVLFLVMYV	VTVLGNCLIV	LLIRLDSRLH	
11-3	MLAR- <u>NN</u>	SLVTEFILAG	LTDREPEFRQ	LFFLFLVIYI	VTMVGNLGLI	ILFGLNSHLH	
	*	*	*	*	*	*	*
OLF2	SPMYFFLSNL	SFLDLCFTTS	CVPQMLANLW	GPKKTISFLD	<u>C</u> SVQIFIFLS	LGTTTECILMK	
OLF3	TPMYFFLTNL	SLVDVSYSATS	VVPQLLAHFL	AENKAIPFQS	<u>C</u> AAQLFFSLA	LGGEIEFVLLA	
11-3	TPMYFFLFNL	SFIDLCYSSV	FTPKMLMNFV	SKKNIISYVG	<u>C</u> MTQLFFFLF	FVISECYILT	
	***	**	*	*	*	*	*
OLF2	VMAF <u>DRY</u> VAV	CQPLHYATII	HPRLCWQLAS	VAWVIGLVGS	VVQTPSTLHL	PFC <u>P</u> DRQVDD	
OLF3	VMAY <u>DRY</u> VAV	CDALRYSAIM	HGGLCARLAI	TSWVSGFISS	PVQTAITFQL	PMCRNKFIDH	
11-3	SMAY <u>DRY</u> VAI	CNPLYKVTHM	SHQVCSMLTF	AAYIMGLAGA	TAHTGCHMLR	TFC <u>S</u> ANIINH	
	**	*****	*	*	*	*	*
OLF2	FV <u>C</u> EPALIR	LSC <u>E</u> DTSYNE	IQVAVASVFI	LVVPLSLILV	SYGAIWAVL	RINSATAWRK	
OLF3	IS <u>C</u> ELLAVVR	LACVDTSSE	VTIMVSSIVL	LMTPLCLVLL	SYIQIISTIL	KIQSREGRKK	
11-3	YL <u>C</u> DILPLLQ	LSC <u>T</u> STYVNE	VVVLIVVGIN	IMVPSCTILI	SYVFIIVTSIL	HIKSTQGRSK	
	*	*	*	*	*	*	*
OLF2	AFGTCSSHLT	VVTLFYSSVI	AVYLQPKNPY	AQGRGKFFGL	FYAVGTPSLN	PLVYTLRNKE	
OLF3	AFHTCASHLT	VVALCYGVAI	FTYIQPHSSP	SVLQEKLFVS	FYAILTPMLN	PMIYSLRNKE	
11-3	AFSTCSSHVI	ALSLEFFGSAA	FMYIKY-SSG	SMEQGVSSV	FYTNVVPMLN	PLIYSLRNKD	
	**	**	*	*	*	**	*
OLF2	IKRALRRLLG	KERDSRESWR	AA				
OLF3	VKGAWQKLLW	KFSGL-TSKL	AT				
11-3	VKVALRKALI	KIQ-RRN--I	-F				
	*	*	*	*			

Figure 31

OLF2 M---DNQ SSTPGFLLG FSEHPGLGRT LFVDVITSYL LTLVGNTLII LLSALDTKLH  
 OLF3 MGT-DNQ TWVSEFILLG LSSDWDTRVS LFVLFVVMYV VTVLGNCLIV LLIRLDSRLH  
 11-4 MTLR-NS SSVTEFILVG LSEQPELQLP LFLFLGIYV FTVVGNLGLI TLIGINPSLH  
 \* \* \* \* \* \*\* \* \* \* \*  
 OLF2 SPMYFFLSNL SFLDLCFTTS CVPQMLANLW GPKKTISFLD CSVQIFIFLS LGTTECILMK  
 OLF3 TPMYFFLTNL SLVDVSYATS VVPQLLAHFL AEHKAIPFQS CAAQLFFSLA LGGIEFVLLA  
 11-4 TPMYFFLFNL SFIDLCYSCV FTPKMLNDFV SES-IISYVG CMTQLFFFCF FVNSECYVLV  
 \*\*\*\*\* \* \* \* \* \*  
 OLF2 VMAFD~~RY~~VAV CQPLHYATII HPRLCWQLAS VAWVIGLVGS VVQTPSTLHL PFCPDRQVDD  
 OLF3 VMAYD~~RY~~VAV CDALRYSAIM HGGLCARLAI TSWVSGFISS PVQTAITFQL PMCRNKFIH  
 11-4 SMAYD~~RY~~VAI CNPLLYMVTM SPRVCFLLMF GSYVVGFGA MAHTGSMLRL TFCDSNVIDH  
 \*\* \*\*\*\*\* \* \* \* \* \*  
 OLF2 FVCEVPALIR LSCEDTSYNE IQVAVASVFI LVVPLSLILV SYGAITWAVL RINSATAWRK  
 OLF3 ISCELLAVVR LACVDTSNE VTIMVSSIVL LMTPLCLVLL SYIQIISTIL KIQSREGRKK  
 11-4 YLCDVLP LLQ LSCTSTHVSE LVFFIVGVFI TMLSSISIVI SYALILSNIL CIPSAEGRSK  
 \* \* \* \* \* \*\* \* \* \* \*  
 OLF2 AFGTCSSHLT VVTLFYSSVI AVYLQPKNPY AQGRGKFFGL FYAVGTPSLN PLVYTLRNKE  
 OLF3 AFHTCASHLT VVALCYGVAI FTYIQPHSSP SVLQEKLFVS FYAILTPMLN PMIYSLRNKE  
 11-4 AFSTWGSII AVALFFGSGT FTYLTTSFPG SMNHGRFASV FYTNVVPMLN PSIYSLRNKD  
 \*\* \* \* \* \* \*  
 OLF2 IKRALRRLG KERDSRESWR AA  
 OLF3 VKGAWQKLLW KFSGL-TSKL AT  
 11-4 DKLALGKTL- K----R--VL -F  
 \* \* \* \*



Attorney's Docket No.:  
Client's Ref. No.:

## COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **NOVEL G PROTEIN-COUPLED RECEPTORS** the specification of which:

- ☒ is attached hereto.  
☐ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_ and was amended on \_\_\_\_\_  
☐ was described and claimed in PCT International Application No. \_\_\_\_\_ filed on \_\_\_\_\_ and as amended under PCT Article 19 on \_\_\_\_\_.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status
-----------------	-------------	--------

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
Japan	10/288565	October 9, 1998	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Japan	10/347546	December 7, 1998	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Japan	10/363537	December 21, 1998	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PCT	PCT/JP99/05578	October 8, 1999	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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153-2, Nagai, Niihari-mura, Niihari-gun,  
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Attorney's Docket No.:  
Client's Ref. No.:

**Combined Declaration and Power of Attorney**

Page 3 of 3 Pages

3-00

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Inventor's Signature:



Date: December 22, 2000

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Ibaraki 300-4101 Japan

Citizenship:

Japan

JPX

Post Office Address:

c/o Chugai Research Institute for Molecular  
Medicine, Inc.  
153-2, Nagai, Niihari-mura, Niihari-gun,  
Ibaraki 300-4101 Japan

## SEQUENCE LISTING

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9/66

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15/66

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 gtgcctcttg ttatcaagct ggctgcaca gatacatacc tcacaggaat actgattgtg 600  
 accaatagtg gaaccatctc cctctctgtt ttcttgccg tggtcacctc ctatatggtc 660  
 atcctgggtt ctcttcgaaa aactcagct gaaggcgcc agaaagccct gtctacctgc 720  
 tcggcccaact tcatggtggt tgccctcttc tttgggcat gtatcttcat ctatactcgg 780  
 ccagacacca gcttctccat tgacaagggt gtgtctgtct tctacacagt ggtcaccct 840  
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 ctcaggcaga gacaagtttt tttcacgaaa tcatatacat aa 942

<210> 22

<211> 942

<212> DNA

<213> Homo sapiens

<400> 22

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 ggaaacctgc ttattttaat cactgtctgg gcagacccaa ggctccatgc ccgccccatg 180  
 tacatctttc ttgggtgttct ctcagtcatt gatatgagca tctcctccat cattgtccct 240  
 cgcctcatga tgaacttcac tttaggtgtc aaacccatcc catttggtgg ctgtgttgct 300  
 caactctatt tctatcactt cctgggcagc acccagtgtc tctctacac cctaattggc 360  
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 ctgagcgcct tgcttgtggc tggagcctgg atggcaggat ccatccatgg ggctctccag 480  
 gccatcctaa ctttcgcct gccctactgt gggcccaatc aggtggatta cttcttctgt 540  
 gacatccctg cagtgttgag actggcctgt gctgacacaa cagtcaacga gctggtgacg 600  
 tttgtagaca ttgggggtggg ggttgccagt tgcttctccc tgatcctcct ctcctacata 660  
 cagatcattc aggccatcct gagaatccac acagctgatg ggcggcgcgc ggctttttca 720  
 acttgtggag cccatgtaac cgtggtcacc gtgtactatg tgccctgtgc cttcatctac 780  
 ctgaggcctg aaaccaacag cccctggat ggggcagctg ccctagtccc caccggccatc 840  
 actcctttcc tcaacccctt tatctacact ctgcggaacc aagaggtgaa gctggccctg 900  
 aaaagaatgc tcagaagccc aagaactccg agtgaggttt ga 942

<210> 23

<211> 933

<212> DNA

<213> Homo sapiens

<400> 23

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 ctactcagc tggggaacct gctcattctg ctaccatgt gggtgaccc gaagctctgt 180  
 gtcgccccca tgtacattct tctgggagtg ctctattcc tggacatgtg gctctcctca 240  
 gtcaccgttc ctggcttat tttggatttt actccttcca tcaaggctat ccggtttggg 300

ggctgtgtgg ctcaactgta tttctttcac ttcctgggca gcacccagtg cttcctctac 360  
accttgatgg cctatgacag gtacctagca atatgtcagc ccctgcacta ccagtgctc 420  
atgaatggga gggttatgcac agtccttgtg gctggagctt gggtcgccgg ctccatgcat 480  
gggtctatcc aggccacctt gaccttccgc ctgccctact gtgggcecaa tcaggtggat 540  
tactttatct gtgacatccg cgcagtattg agactggcct gtgctgacac aactgtcaat 600  
gagcttgtga cctttgtgga cgtcagggtg gtggccgcca gttgcttcat gttaattctg 660  
ctctcctatg ccaacatagt ccatgccatc ctgaagatac gcaccgctga tgggaggcgc 720  
cgggccttct ccacctgtgg ctcccaccta atcggtgtca cagtctacta tgtcccctgt 780  
atcttcatct accttagggc tggtccaaa gaccccttg atggggcagc ggctgtgttt 840  
tacctgttg tcaactcatt actgaacccc ctcatctata cactgaggaa ccaggaagtg 900  
aagtctgccc tgaagaggat aacagcaggt tga 933

<210> 24

<211> 1060

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (17)..(892)

<400> 24

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Met Thr Met Glu Asn Tyr Ser Met Ala Ala Gln Phe

1

5

10

gtc tta gat ggt tta aca cag caa gca gag ctc cag ctg ccc ctc ttc 100

Val Leu Asp Gly Leu Thr Gln Gln Ala Glu Leu Gln Leu Pro Leu Phe

15

20

25

ctc ctg ttc ctg gga atc tat gtg gtc aca gta gtg ggc aac ctg ggc 148

Leu Leu Phe Leu Gly Ile Tyr Val Val Thr Val Val Gly Asn Leu Gly

30

35

40

atg att ctc ctg att gca gtc agc cct cta ctt cac acc ccc atg tac 196

Met Ile Leu Leu Ile Ala Val Ser Pro Leu Leu His Thr Pro Met Tyr

45

50

55

60

tat ttc ctc agc agc ttg tcc ttc gtc gat ttc tgc tat tcc tct gtc 244

Tyr Phe Leu Ser Ser Leu Ser Phe Val Asp Phe Cys Tyr Ser Ser Val

65

70

75

att act ccc aaa atg ctg gtg aac ttc cta gga aag aag aat aca atc 292

Ile Thr Pro Lys Met Leu Val Asn Phe Leu Gly Lys Lys Asn Thr Ile

80

85

90

ctt tac tct gag tgc atg gtc cag ctc ttt ttc ttt gtg gtc ttt gtg 340

Leu Tyr Ser Glu Cys Met Val Gln Leu Phe Phe Phe Val Val Phe Val

95

100

105

gtg gct gag ggt tac ctc ctg act gcc atg gca tat gat cgc tat gtt 388

Val Ala Glu Gly Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Val

110                                      115                                      120  
 gcc atc tgt agc cca ctg ctt tat aat gcg atc atg tcc tca tgg gtc    436  
 Ala Ile Cys Ser Pro Leu Leu Tyr Asn Ala Ile Met Ser Ser Trp Val  
 125                                      130                                      135                                      140  
 tgc tca ctg cta gtg ctg gct gcc ttc ttc ttg ggc ttt ctc tct gcc    484  
 Cys Ser Leu Leu Val Leu Ala Ala Phe Phe Leu Gly Phe Leu Ser Ala  
 145                                      150                                      155  
 ttg act cat aca agt gcc atg atg aaa ctg tcc ttt tgc aaa tcc cac    532  
 Leu Thr His Thr Ser Ala Met Met Lys Leu Ser Phe Cys Lys Ser His  
 160                                      165                                      170  
 att atc aac cat tac ttc tgt gat gtt ctt ccc ctc ctc aat ctc tcc    580  
 Ile Ile Asn His Tyr Phe Cys Asp Val Leu Pro Leu Leu Asn Leu Ser  
 175                                      180                                      185  
 tgc tcc aac aca cac ctc aat gag ctt cta ctt ttt atc att gcg ggg    628  
 Cys Ser Asn Thr His Leu Asn Glu Leu Leu Leu Phe Ile Ile Ala Gly  
 190                                      195                                      200  
 ttt aac acc ttg gtg ccc acc cta gct gtt gct gtc tcc tat gcc ttc    676  
 Phe Asn Thr Leu Val Pro Thr Leu Ala Val Ala Val Ser Tyr Ala Phe  
 205                                      210                                      215                                      220

27/66

atc ctc tac agc atc ctt cac atc cgc tcc tca gag ggc cgg tcc aaa 724

Ile Leu Tyr Ser Ile Leu His Ile Arg Ser Ser Glu Gly Arg Ser Lys

225

230

235

gct ttt gga aca tgc agc tct cat ctc atg gct gtg gtg atc ttc ttt 772

Ala Phe Gly Thr Cys Ser Ser His Leu Met Ala Val Val Ile Phe Phe

240

245

250

ggg tcc att acc ttc atg tat ttc aag ccc cct tca agt aac tcc ctg 820

Gly Ser Ile Thr Phe Met Tyr Phe Lys Pro Pro Ser Ser Asn Ser Leu

255

260

265

gac cag gag aag gtg tcc tct gtg ttc tac acc acg gtg atc ccc atg 868

Asp Gln Glu Lys Val Ser Ser Val Phe Tyr Thr Thr Val Ile Pro Met

270

275

280

ctg aac cct tta ata tac agt ctg taatcacagc actttggaag gctgaggcag 922

Leu Asn Pro Leu Ile Tyr Ser Leu

285

290

ggttgcttga gtccagtttg agaccatcct ggggaacata gtgcgatctt gtttctttcc 982

actgcctaaa aacttcaatg ctcaatttta cttgcaattt cctcttctg acatggagaa 1042

tggttgcttg gaatgttc

1060

<210> 25

<211> 1069

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (18).. (956)

<400> 25

atTTTTgaag acaaaaa atg ctg gct aga aac aac tcc tta gtg act gaa 50

Met Leu Ala Arg Asn Asn Ser Leu Val Thr Glu

1

5

10

ttt att ctt gct gga tta aca gat cgt cca gag ttc tgg caa ccc ttc 98

Phe Ile Leu Ala Gly Leu Thr Asp Arg Pro Glu Phe Trp Gln Pro Phe

15

20

25

ttt ttc ctg ttc cta gtg atc tac att gtc acc atg gta ggc aac ctt 146

Phe Phe Leu Phe Leu Val Ile Tyr Ile Val Thr Met Val Gly Asn Leu

30

35

40

ggc ttg atc act ctt ttc ggt cta aat tct cac ctc cac aca cca atg 194

Gly Leu Ile Thr Leu Phe Gly Leu Asn Ser His Leu His Thr Pro Met

45

50

55

tac tat ttc ctc ttc aat ctc tcc ttc att gat ctc tgt tac tcc tct 242  
 Tyr Tyr Phe Leu Phe Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Ser  
 60 65 70 75

gtt ttc act ccc aaa atg cta atg aac ttt gtg tca aaa aag aat att 290  
 Val Phe Thr Pro Lys Met Leu Met Asn Phe Val Ser Lys Lys Asn Ile  
 80 85 90

atc tcc aat gtt ggg tgc atg act cgg ctg ttt ttc ttt ctc ttt ttc 338  
 Ile Ser Asn Val Gly Cys Met Thr Arg Leu Phe Phe Phe Leu Phe Phe  
 95 100 105

gtc atc tct gaa tgt tac atg ttg acc tca atg gca tat gat cgc tat 386  
 Val Ile Ser Glu Cys Tyr Met Leu Thr Ser Met Ala Tyr Asp Arg Tyr  
 110 115 120

gtg gcc atc tgt aat cca ttg ctg tat aag gtc acc atg tcc cat cag 434  
 Val Ala Ile Cys Asn Pro Leu Leu Tyr Lys Val Thr Met Ser His Gln  
 125 130 135

gtc tgt tct atg ctc act ttt gct gct tac ata atg gga ttg gct gga 482  
 Val Cys Ser Met Leu Thr Phe Ala Ala Tyr Ile Met Gly Leu Ala Gly  
 140 145 150 155

gcc acg gcc cac acc ggg tgc atg ttt aga ctc acc ttc tgc agt gct 530



Ala Thr Ala His Thr Gly Cys Met Phe Arg Leu Thr Phe Cys Ser Ala  
 160 165 170

aat atc att aac cat tac ttg tgt gac ata ctc ccc ctc ctc cag ctt 578  
 Asn Ile Ile Asn His Tyr Leu Cys Asp Ile Leu Pro Leu Leu Gln Leu  
 175 180 185

tcc tgc acc agc acc tat gtc aac gag gtg gtt gtt ctc att gtt gtg 626  
 Ser Cys Thr Ser Thr Tyr Val Asn Glu Val Val Val Leu Ile Val Val  
 190 195 200

ggt act aat atc acg gta ccc agt tgt acc atc ctc att tct tat gtt 674  
 Gly Thr Asn Ile Thr Val Pro Ser Cys Thr Ile Leu Ile Ser Tyr Val  
 205 210 215

ttc att gtc act agc att ctt cat atc aaa tcc act caa gga aga tca 722  
 Phe Ile Val Thr Ser Ile Leu His Ile Lys Ser Thr Gln Gly Arg Ser  
 220 225 230 235

aaa gcc ttc agt act tgt agc tct cat gtc att gct ctg tct ctg ttt 770  
 Lys Ala Phe Ser Thr Cys Ser Ser His Val Ile Ala Leu Ser Leu Phe  
 240 245 250

ttt ggg tca gcg gca ttc atg tat att aaa tat tct tct gga tct atg 818  
 Phe Gly Ser Ala Ala Phe Met Tyr Ile Lys Tyr Ser Ser Gly Ser Met  
 255 260 265

gag cag gga aaa gtt ttt tct gtt ttc tac act aat gtg gtg ccc atg 866  
 Glu Gln Gly Lys Val Phe Ser Val Phe Tyr Thr Asn Val Val Pro Met  
 270 275 280

ctc aat ccc ctc atc tac agt ttg agg aac aag gat gtc aaa gtt gca 914  
 Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Asp Val Lys Val Ala  
 285 290 295

ctg agg aaa gct ctg att aaa att cag agg aga aat ata ttc 956  
 Leu Arg Lys Ala Leu Ile Lys Ile Gln Arg Arg Asn Ile Phe  
 300 305 310

taattagaag cagtaatgat gtaaaacaat tgaaggactt caaatTTTTA ttagtgtttt 1016

tcatgaagag atTTTgttTgt ttctacagat ggtgttatgt gtgatttaaat aaa 1069

<210> 26

<211> 1069

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (18)..(956)

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	1	5	10
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Phe Ile Leu Ala Gly Leu Thr Asp Arg Pro Glu Phe Arg Gln Pro Leu

15                      20                      25

Phe Phe Leu Phe Leu Val Ile Tyr Ile Val Thr Met Val Gly Asn Leu

30                      35                      40

Gly Leu Ile Ile Leu Phe Gly Leu Asn Ser His Leu His Thr Pro Met

45                      50                      55

Tyr Tyr Phe Leu Phe Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Ser

60                      65                      70                      75

Val Phe Thr Pro Lys Met Leu Met Asn Phe Val Ser Lys Lys Asn Ile

80                      85                      90

atc tcc tat gtt ggg tgc atg act cag ctg ttt ttc ttt ctc ttt ttt 338

Ile Ser Tyr Val Gly Cys Met Thr Gln Leu Phe Phe Phe Leu Phe Phe

95

100

105

gtc atc tct gaa tgc tac ata ttg acc tca atg gca tat gat cgc tat 386

Val Ile Ser Glu Cys Tyr Ile Leu Thr Ser Met Ala Tyr Asp Arg Tyr

110

115

120

gtg gcc atc tgt aat cca ttg ctg tat aag gtc acc atg tcc cat cag 434

Val Ala Ile Cys Asn Pro Leu Leu Tyr Lys Val Thr Met Ser His Gln

125

130

135

gtc tgt tct atg ctc act ttt gct gct tac ata atg gga ttg gct gga 482

Val Cys Ser Met Leu Thr Phe Ala Ala Tyr Ile Met Gly Leu Ala Gly

140

145

150

155

gcc acg gcc cac acc ggg tgc atg ctt aga ctc acc ttc tgc agt gct 530

Ala Thr Ala His Thr Gly Cys Met Leu Arg Leu Thr Phe Cys Ser Ala

160

165

170

aat atc atc aac cat tac ttg tgt gac ata ctc ccc ctc ctc cag ctt 578

Asn Ile Ile Asn His Tyr Leu Cys Asp Ile Leu Pro Leu Leu Gln Leu

175

180

185

tcc tgc acc agc acc tat gtc aac gag gtg gtt gtt ctc att gtt gtg 626

Ser Cys Thr Ser Thr Tyr Val Asn Glu Val Val Val Leu Ile Val Val

190	195	200	
ggt att aat atc atg gta ccc agt tgt acc atc ctc att tct tat gtt    674			
Gly Ile Asn Ile Met Val Pro Ser Cys Thr Ile Leu Ile Ser Tyr Val			
205	210	215	
ttc att gtc act agc att ctt cat atc aaa tcc act caa gga aga tca    722			
Phe Ile Val Thr Ser Ile Leu His Ile Lys Ser Thr Gln Gly Arg Ser			
220	225	230	235
aaa gcc ttc agt act tgt agc tct cat gtc att gct ctg tct ctg ttt    770			
Lys Ala Phe Ser Thr Cys Ser Ser His Val Ile Ala Leu Ser Leu Phe			
240	245	250	
ttt ggg tca gcg gca ttc atg tat att aaa tat tct tct gga tct atg    818			
Phe Gly Ser Ala Ala Phe Met Tyr Ile Lys Tyr Ser Ser Gly Ser Met			
255	260	265	
gag cag gga aaa gtt tct tct gtt ttc tac act aat gtg gtg ccc atg    866			
Glu Gln Gly Lys Val Ser Ser Val Phe Tyr Thr Asn Val Val Pro Met			
270	275	280	
ctc aat cct ctc atc tac agt ttg agg aac aag gat gtc aaa gtt gca    914			
Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Asp Val Lys Val Ala			
285	290	295	

ctg agg aaa gct ctg att aaa att cag aga aga aat ata ttc 956

Leu Arg Lys Ala Leu Ile Lys Ile Gln Arg Arg Asn Ile Phe

300

305

310

taattagaag cagtaataat gtaaaacgat tgaagaactt taaattttta ttagtggtgtt 1016

ccatgaagag attttggtgt ttctacagat ggtggtatgt gtgatttaaat aaa 1069

<210> 27

<211> 976

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (19).. (945)

<400> 27

acagctcgcc aagagaga atg act ctg aga aac agc tcc tca gtg act gag 51

Met Thr Leu Arg Asn Ser Ser Ser Val Thr Glu

1

5

10

ttt atc ctt gtg gga tta tca gaa cag cca gag ctc cag ctc cct ctt 99

Phe Ile Leu Val Gly Leu Ser Glu Gln Pro Glu Leu Gln Leu Pro Leu

15

20

25

ttc ctt cta ttc tta ggg atc tat gtg ttc act gtg gtg ggc aac ttg 147

Phe Leu Leu Phe Leu Gly Ile Tyr Val Phe Thr Val Val Gly Asn Leu

30

35

40

ggc ttg atc acc tta att ggg ata aat cct agc ctt cac acc ccc atg 195

Gly Leu Ile Thr Leu Ile Gly Ile Asn Pro Ser Leu His Thr Pro Met

45

50

55

tac ttt ttc ctc ttc aac ttg tcc ttt ata gat ctc tgt tat tcc tgt 243

Tyr Phe Phe Leu Phe Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Cys

60

65

70

75

gtg ttt acc ccc aaa atg ctg aat gac ttt gtt tca gaa agt atc atc 291

Val Phe Thr Pro Lys Met Leu Asn Asp Phe Val Ser Glu Ser Ile Ile

80

85

90

tct tat gtg gga tgt atg act cag cta ttt ttc ttc tgt ttc ttt gtc 339

Ser Tyr Val Gly Cys Met Thr Gln Leu Phe Phe Phe Cys Phe Phe Val

95

100

105

aat tct gag tgc tat gtg ttg gta tca atg gcc tat gat cgc tat gtg 387

Asn Ser Glu Cys Tyr Val Leu Val Ser Met Ala Tyr Asp Arg Tyr Val

110

115

120

gcc atc tgc aac ccc ctg ctc tac atg gtc acc atg tcc cca agg gtc 435

Ala Ile Cys Asn Pro Leu Leu Tyr Met Val Thr Met Ser Pro Arg Val

125

130

135

tgc ttt ctg ctg atg ttt ggt tcc tat gtg gta ggg ttt gct ggg gcc 483

Cys Phe Leu Leu Met Phe Gly Ser Tyr Val Val Gly Phe Ala Gly Ala

140

145

150

155

atg gcc cac act gga agc atg ctg cga ctg acc ttc tgt gat tcc aac 531

Met Ala His Thr Gly Ser Met Leu Arg Leu Thr Phe Cys Asp Ser Asn

160

165

170

gtc att gac cat tat ctg tgt gac gtt ctc ccc ctc ttg cag ctc tcc 579

Val Ile Asp His Tyr Leu Cys Asp Val Leu Pro Leu Leu Gln Leu Ser

175

180

185

tgc acc agc acc cat gtc agt gag ctg gta ttt ttc att gtt gtt gga 627

Cys Thr Ser Thr His Val Ser Glu Leu Val Phe Phe Ile Val Val Gly

190

195

200

gta atc acc atg cta tcc agc ata agc atc gtc atc tct tac gct ttg 675

Val Ile Thr Met Leu Ser Ser Ile Ser Ile Val Ile Ser Tyr Ala Leu

205

210

215

ata ctc tcc aac atc ctc tgt att cct tct gca gag ggc aga tcc aaa 723

Ile Leu Ser Asn Ile Leu Cys Ile Pro Ser Ala Glu Gly Arg Ser Lys

220

225

230

235



gcc ttt agc aca tgg ggc tcc cac ata att gct gtt gct ctg ttt ttt 771

Ala Phe Ser Thr Trp Gly Ser His Ile Ile Ala Val Ala Leu Phe Phe

240

245

250

ggg tca ggg aca ttc acc tac tta aca aca tct ttt cct ggc tct atg 819

Gly Ser Gly Thr Phe Thr Tyr Leu Thr Thr Ser Phe Pro Gly Ser Met

255

260

265

aac cat ggc aga ttt gcc tca gtc ttt tac acc aat gtg gtt ccc atg 867

Asn His Gly Arg Phe Ala Ser Val Phe Tyr Thr Asn Val Val Pro Met

270

275

280

ctt aac cct tcg atc tac agt ttg agg aat aag gat gat aaa ctt gcc 915

Leu Asn Pro Ser Ile Tyr Ser Leu Arg Asn Lys Asp Asp Lys Leu Ala

285

290

295

ctg ggc aaa acc ctg aag aga gtg ctc ttc taatgggtct cttcatatca 965

Leu Gly Lys Thr Leu Lys Arg Val Leu Phe

300

305

ctggcaaccg a

976

<210> 28

<211> 292

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 28

Met Thr Met Glu Asn Tyr Ser Met Ala Ala Gln Phe Val Leu Asp Gly

1 5 10 15

Leu Thr Gln Gln Ala Glu Leu Gln Leu Pro Leu Phe Leu Leu Phe Leu

20 25 30

Gly Ile Tyr Val Val Thr Val Val Gly Asn Leu Gly Met Ile Leu Leu

35 40 45

Ile Ala Val Ser Pro Leu Leu His Thr Pro Met Tyr Tyr Phe Leu Ser

50 55 60

Ser Leu Ser Phe Val Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys

65 70 75 80

Met Leu Val Asn Phe Leu Gly Lys Lys Asn Thr Ile Leu Tyr Ser Glu

85 90 95

Cys Met Val Gln Leu Phe Phe Phe Val Val Phe Val Val Ala Glu Gly

100 105 110

Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys Ser

115	120	125
Pro Leu Leu Tyr Asn Ala Ile Met Ser Ser Trp Val Cys Ser Leu Leu		
130	135	140
Val Leu Ala Ala Phe Phe Leu Gly Phe Leu Ser Ala Leu Thr His Thr		
145	150	155
Ser Ala Met Met Lys Leu Ser Phe Cys Lys Ser His Ile Ile Asn His		
165	170	175
Tyr Phe Cys Asp Val Leu Pro Leu Leu Asn Leu Ser Cys Ser Asn Thr		
180	185	190
His Leu Asn Glu Leu Leu Leu Phe Ile Ile Ala Gly Phe Asn Thr Leu		
195	200	205
Val Pro Thr Leu Ala Val Ala Val Ser Tyr Ala Phe Ile Leu Tyr Ser		
210	215	220
Ile Leu His Ile Arg Ser Ser Glu Gly Arg Ser Lys Ala Phe Gly Thr		
225	230	235
Cys Ser Ser His Leu Met Ala Val Val Ile Phe Phe Gly Ser Ile Thr		
245	250	255

270

285

•

〈213〉 Homo sapiens

15

30

45

Phe Gly Leu Asn Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Phe

50 55 60

Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Ser Val Phe Thr Pro Lys

65 70 75 80

Met Leu Met Asn Phe Val Ser Lys Lys Asn Ile Ile Ser Asn Val Gly

85 90 95

Cys Met Thr Arg Leu Phe Phe Phe Leu Phe Phe Val Ile Ser Glu Cys

100 105 110

Tyr Met Leu Thr Ser Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys Asn

115 120 125

Pro Leu Leu Tyr Lys Val Thr Met Ser His Gln Val Cys Ser Met Leu

130 135 140

Thr Phe Ala Ala Tyr Ile Met Gly Leu Ala Gly Ala Thr Ala His Thr

145 150 155 160

Gly Cys Met Phe Arg Leu Thr Phe Cys Ser Ala Asn Ile Ile Asn His

165 170 175

Tyr Leu Cys Asp Ile Leu Pro Leu Leu Gln Leu Ser Cys Thr Ser Thr

180 185 190

Tyr Val Asn Glu Val Val Val Leu Ile Val Val Gly Thr Asn Ile Thr

195

200

205

Val Pro Ser Cys Thr Ile Leu Ile Ser Tyr Val Phe Ile Val Thr Ser

210

215

220

Ile Leu His Ile Lys Ser Thr Gln Gly Arg Ser Lys Ala Phe Ser Thr

225

230

235

240

Cys Ser Ser His Val Ile Ala Leu Ser Leu Phe Phe Gly Ser Ala Ala

245

250

255

Phe Met Tyr Ile Lys Tyr Ser Ser Gly Ser Met Glu Gln Gly Lys Val

260

265

270

Phe Ser Val Phe Tyr Thr Asn Val Val Pro Met Leu Asn Pro Leu Ile

275

280

285

Tyr Ser Leu Arg Asn Lys Asp Val Lys Val Ala Leu Arg Lys Ala Leu

290

295

300

Ile Lys Ile Gln Arg Arg Asn Ile Phe

305

310

<210> 30

<211> 313

<212> PRT

<213> Homo sapiens

<400> 30

Met Leu Ala Arg Asn Asn Ser Leu Val Thr Glu Phe Ile Leu Ala Gly

1 5 10 15

Leu Thr Asp Arg Pro Glu Phe Arg Gln Pro Leu Phe Phe Leu Phe Leu

20 25 30

Val Ile Tyr Ile Val Thr Met Val Gly Asn Leu Gly Leu Ile Ile Leu

35 40 45

Phe Gly Leu Asn Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Phe

50 55 60

Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Ser Val Phe Thr Pro Lys

65 70 75 80

Met Leu Met Asn Phe Val Ser Lys Lys Asn Ile Ile Ser Tyr Val Gly

85 90 95

Cys Met Thr Gln Leu Phe Phe Phe Leu Phe Phe Val Ile Ser Glu Cys

100 105 110

125

140

160

175

190

205

220

240

255



270

285

300

310

<213> Homo sapiens

15

30

Gly Ile Tyr Val Phe Thr Val Val Gly Asn Leu Gly Leu Ile Thr Leu

35

40

45

Ile Gly Ile Asn Pro Ser Leu His Thr Pro Met Tyr Phe Phe Leu Phe

50

55

60

Asn Leu Ser Phe Ile Asp Leu Cys Tyr Ser Cys Val Phe Thr Pro Lys

65

70

75

80

Met Leu Asn Asp Phe Val Ser Glu Ser Ile Ile Ser Tyr Val Gly Cys

85

90

95

Met Thr Gln Leu Phe Phe Phe Cys Phe Phe Val Asn Ser Glu Cys Tyr

100

105

110

Val Leu Val Ser Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys Asn Pro

115

120

125

Leu Leu Tyr Met Val Thr Met Ser Pro Arg Val Cys Phe Leu Leu Met

130

135

140

Phe Gly Ser Tyr Val Val Gly Phe Ala Gly Ala Met Ala His Thr Gly

145

150

155

160

Ser Met Leu Arg Leu Thr Phe Cys Asp Ser Asn Val Ile Asp His Tyr

165

170

175

Leu Cys Asp Val Leu Pro Leu Leu Gln Leu Ser Cys Thr Ser Thr His

180

185

190

Val Ser Glu Leu Val Phe Phe Ile Val Val Gly Val Ile Thr Met Leu

195

200

205

Ser Ser Ile Ser Ile Val Ile Ser Tyr Ala Leu Ile Leu Ser Asn Ile

210

215

220

Leu Cys Ile Pro Ser Ala Glu Gly Arg Ser Lys Ala Phe Ser Thr Trp

225

230

235

240

Gly Ser His Ile Ile Ala Val Ala Leu Phe Phe Gly Ser Gly Thr Phe

245

250

255

Thr Tyr Leu Thr Thr Ser Phe Pro Gly Ser Met Asn His Gly Arg Phe

260

265

270

Ala Ser Val Phe Tyr Thr Asn Val Val Pro Met Leu Asn Pro Ser Ile

275

280

285

Tyr Ser Leu Arg Asn Lys Asp Asp Lys Leu Ala Leu Gly Lys Thr Leu

290

295

300

Lys Arg Val Leu Phe

305

&lt;210&gt; 32

&lt;211&gt; 762

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (17).. (760)

&lt;400&gt; 32

aaatgcctaa agaaga atg acc atg gaa aat tat tct atg gca gct cag ttt 52

Met Thr Met Glu Asn Tyr Ser Met Ala Ala Gln Phe

1

5

10

gtc tta gat ggt tta aca cag caa gca gag ctc cag ctg ccc ctc ttc 100

Val Leu Asp Gly Leu Thr Gln Gln Ala Glu Leu Gln Leu Pro Leu Phe

15

20

25

ctc ctg ttc ctg gga atc tat gtg gtc aca gta gtg ggc aac ctg ggc 148

Leu Leu Phe Leu Gly Ile Tyr Val Val Thr Val Val Gly Asn Leu Gly

30

35

40

atg att ctc ctg att gca gtc agc cct cta ctt cac acc ccc atg tac 196

Met	Ile	Leu	Leu	Ile	Ala	Val	Ser	Pro	Leu	Leu	His	Thr	Pro	Met	Tyr	
45					50					55					60	
tat	ttc	ctc	agc	agc	ttg	tcc	ttc	gtc	gat	ttc	tgc	tat	tcc	tct	gtc	244
Tyr	Phe	Leu	Ser	Ser	Leu	Ser	Phe	Val	Asp	Phe	Cys	Tyr	Ser	Ser	Val	
					65				70					75		
att	act	ccc	aaa	atg	ctg	gtg	aac	ttc	cta	gga	aag	aag	aat	aca	atc	292
Ile	Thr	Pro	Lys	Met	Leu	Val	Asn	Phe	Leu	Gly	Lys	Lys	Asn	Thr	Ile	
				80				85					90			
ctt	tac	tct	gag	tgc	atg	gtc	cag	ctc	ttt	ttc	ttt	gtg	gtc	ttt	gtg	340
Leu	Tyr	Ser	Glu	Cys	Met	Val	Gln	Leu	Phe	Phe	Phe	Val	Val	Phe	Val	
				95				100					105			
gtg	gct	gag	ggt	tac	ctc	ctg	act	gcc	atg	gca	tat	gat	cgc	tat	gtt	388
Val	Ala	Glu	Gly	Tyr	Leu	Leu	Thr	Ala	Met	Ala	Tyr	Asp	Arg	Tyr	Val	
				110				115					120			
gcc	atc	tgt	agc	cca	ctg	ctt	tat	aat	gcg	atc	atg	tcc	tca	tgg	gtc	436
Ala	Ile	Cys	Ser	Pro	Leu	Leu	Tyr	Asn	Ala	Ile	Met	Ser	Ser	Trp	Val	
125					130					135				140		
tgc	tca	ctg	cta	gtg	ctg	gct	gcc	ttc	ttc	ttg	ggc	ttt	ctc	tct	gcc	484
Cys	Ser	Leu	Leu	Val	Leu	Ala	Ala	Phe	Phe	Leu	Gly	Phe	Leu	Ser	Ala	
					145					150				155		

ttg act cat aca agt gcc atg atg aaa ctg tcc ttt tgc aaa tcc cac 532

Leu Thr His Thr Ser Ala Met Met Lys Leu Ser Phe Cys Lys Ser His

160

165

170

att atc aac cat tac ttc tgt gat gtt ctt ccc ctc ctc aat ctc tcc 580

Ile Ile Asn His Tyr Phe Cys Asp Val Leu Pro Leu Leu Asn Leu Ser

175

180

185

tgc tcc aac aca cac ctc aat gag ctt cta ctt ttt atc att gcg ggg 628

Cys Ser Asn Thr His Leu Asn Glu Leu Leu Leu Phe Ile Ile Ala Gly

190

195

200

ttt aac acc ttg gtg ccc acc cta gct gtt gct gtc tcc tat gcc ttc 676

Phe Asn Thr Leu Val Pro Thr Leu Ala Val Ala Val Ser Tyr Ala Phe

205

210

215

220

atc ctc tac agc atc ctt cac atc cgc tcc tca gag ggc cgg tcc aaa 724

Ile Leu Tyr Ser Ile Leu His Ile Arg Ser Ser Glu Gly Arg Ser Lys

225

230

235

gct ttt gga aca tgc agc tct cat ctc atg gct gtg gt 762

Ala Phe Gly Thr Cys Ser Ser His Leu Met Ala Val

240

245

<213> Homo sapiens

100                      105                      110

Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys Ser

115

120

125

Pro Leu Leu Tyr Asn Ala Ile Met Ser Ser Trp Val Cys Ser Leu Leu

130

135

140

Val Leu Ala Ala Phe Phe Leu Gly Phe Leu Ser Ala Leu Thr His Thr

145

150

155

160

Ser Ala Met Met Lys Leu Ser Phe Cys Lys Ser His Ile Ile Asn His

165

170

175

Tyr Phe Cys Asp Val Leu Pro Leu Leu Asn Leu Ser Cys Ser Asn Thr

180

185

190

His Leu Asn Glu Leu Leu Leu Phe Ile Ile Ala Gly Phe Asn Thr Leu

195

200

205

Val Pro Thr Leu Ala Val Ala Val Ser Tyr Ala Phe Ile Leu Tyr Ser

210

215

220

Ile Leu His Ile Arg Ser Ser Glu Gly Arg Ser Lys Ala Phe Gly Thr

225

230

235

240

Cys Ser Ser His Leu Met Ala Val



245

&lt;210&gt; 34

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

&lt;400&gt; 34

gaagagcagt gaggtccat gttaagg

27

&lt;210&gt; 35

&lt;211&gt; 28

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

&lt;400&gt; 35

cagcagcttg tccttcgtcg atttctgc

28

<210> 36

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 36

gctagggtgg gcaccaaggt gttaaacc

29

<210> 37

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 37

tgcaaaagga cagtttcac atggcac

27

<210> 38

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 38

caaagaactc acccaaattc ctacagct

28

<210> 39

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 39

catggtaggc aaccttggct tgatcac

27

<210> 40

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 40

gtttattaaa tcacacataa caccatctg

29

<210> 41

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 41

29

&lt;211&gt; 28

<212> DNA

### <213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Description of Artificial Sequence: Artificially synthesized primer sequence

<400> 42

28

&lt;210&gt; 43

&lt;211&gt; 27

## <212> DNA

### <213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Description of Artificial Sequence: Artificially synthesized primer sequence

&lt;400&gt; 43

catggtaggc aaccttggct tgatcat

27

<210> 44

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 44

gtttattaaa tcacacataa caccatctg

29

<210> 45

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 45

cagagacaga gcaatgacat gagagctac

29

<210> 46

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 46

ccagacagct cgccaagaga gaatgac

27

<210> 47

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 47

cctttataga tctctgttat tcctgtgtg

29

<210> 48

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 48

tcggttgcca gtgatatgaa gagaccc

27

<210> 49

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Artificially  
synthesized primer sequence

<400> 49



27

◁213▷ Homo sapiens

ggggtttaac accttggtgc ccaccctagc 450

<210> 51

<211> 637

<212> DNA

<213> Homo sapiens

<400> 51

catggtaggc aaccttggt tgatcaactt tttegggtcta aattctcacc tccacacacc 60

aatgtactat ttctctttca atctctcctt cattgatctc tgttactcct ctgttttcac 120

tcccaaaatg ctaatgaact ttgtgtcaaa aaagaatatt atctccaatg ttgggtgcat 180

gactcggctg tttttctttc tctttttcgt catctctgaa tgttacatgt tgacctcaat 240

ggcatatgat cgctatgtgg ccatctgtaa tccattgctg tataaggcca ccatgtccca 300

tcaggctctg tctatgctca cttttgctgc ttacataatg ggattggctg gagccacggc 360

ccacaccggg tgcattgttta gactcacctt ctgcagtgt aatatcatta accattactt 420

gtgtgacata ctccccctcc tccagctttc ctgcaccagc acctatgtca acgaggtggt 480

tgttctcatt gttgtgggta ctaatatcac ggtaccacgt tgtaccatcc tcatttctta 540

tgttttcatt gtcactagca ttcttcatat caaatccact caaggaagat caaaagcctt 600

cagtacttgt agctctcatg tcattgctct gtctctg

637

<210> 52

<211> 637

<212> DNA

<213> Homo sapiens

<400> 52

catggtaggc aaccttggct tgatcattct tttcgggtcta aattctcacc tccacacacc 60

aatgtactat ttctctttca atctctcctt cattgatctc tgttactcct ctgtttttcac 120

tcccaaaatg ctaatgaact ttgtatcaaa aaagaatatt atctcctatg ttgggtgcat 180

gactcagctg tttttctttc tcttttttgt catctctgaa tgctacatat tgacctcaat 240

ggcatatgat cgctatgtgg ccatctgtaa tccattgctg tataaggtca ccatgtccca 300

tcaggctctgt tctatgctca cttttgctgc ttacataatg ggattggctg gagccacggc 360

ccacaccggg tgcattgctta gactcacctt ctgcagtgtc aatatcatca accattactt 420

gtgtgacata ctccccctcc tccagctttc ctgcaccagg accatatgtca acgaggtggt 480

gtttctcatt gttgtgggta ttaatatcat ggtaccaggt tgtaccatcc tcattttctta 540

tgttttcatt gtcactagca ttcttcatat caaatccact caaggaagat caaaagcctt 600

cagtacttgt agctctcatg tcattgctct gtctctg 637

<210> 53

<211> 509

<212> DNA

<213> Homo sapiens

<400> 53

cctttataga tctctgttat tctgtgtgt ttacccccaa aatgctgaat gactttgttt 60

cagaaagtat catctcttat gtgggatgta tgactcagct attttcttc tgtttctttg 120

tcaattctga gtgctatgtg ttggtatcaa tggcctatga tegctatgtg gccatctgca 180

acccctgct ctacatggtc accatgtccc caagggtctg ctttctgctg atgtttggtt 240

cctatgtggt agggtttgct ggggccatgg cccacactgg aagcatgctg cgactgacct 300

tctgtgattc caacgtcatt gaccattatc tgtgtgacgt tctccccctc ttgcagctct 360

cctgcaccag cacccatgtc agtgagctgg tatttttcat tgttgttgga gtaatcacca 420

tgctatccag cataagcatc gtcattcttt acgttttgat actctccaac atcctctgta 480

ttccttctgc agagggcaga tccaaagcc

509